# Mechanism of Bromination of 4(3*H*)-Pyrimidinone and Its *N*-Methyl Derivatives in Aqueous Acidic Solution. Unusual Acidity Dependence in the Dehydration of Observable Intermediates

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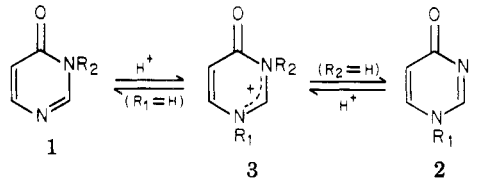
The bromination of 4(3*H*)-pyrimidinone, 1-methyl-4-pyrimidinone, 3-methyl-4-pyrimidinone, and the 1,4-dihydro-1,3-dimethyl-4-oxopyrimidinium cation in aqueous acidic media have been examined. The reactions lead to overall substitution at the 5 position by way of an addition–elimination mechanism involving observable *cationic* intermediates. The kinetics of dehydration of these intermediates exhibit unusual acidity dependence in that the rates *decrease* somewhat with *increasing* acid concentration. Kinetic primary and solvent isotope effects accompanying dehydration were also measured. The quaternary cation, mentioned above, probably undergoes bromine attack by way of its pseudobase. Analogously the other three substrates probably react via covalent hydrates.

We have undertaken mechanistic studies of the aqueous bromination of mono- and dioxopyrimidines to gain insight into the reactivity of these derivatives toward electrophilic attack. Previous work implicates addition–elimination mechanisms in the bromination of 2(1*H*)-pyrimidinones[1] and of uracils.[2] In the former case *rapid* bromine attack upon a covalent hydrate of the pyrimidinone leads to the formation of an observable intermediate which undergoes *slow* acid-catalyzed dehydration to give the substitution product, a 5-bromo-2(1*H*)-pyrimidinone.[1] For uracils direct attack by bromine also leads to the formation of an observable intermediate which likewise undergoes acid-catalyzed dehydration to the appropriate 5-bromouracil.[2] The bromination of 4(3*H*)-quinazolinone also involves electrophilic attack upon a covalent hydrate of the substrate, but no long lived intermediate is involved.[3]

The present paper describes related studies on the bromination of 4(3*H*)-pyrimidinone (**1**, $R_2$ = H) and simple *N*-methyl derivatives. The results are consistent with the operation of an addition–elimination mechanism similar to that involved in the bromination of 2(1*H*)-pyrimidinone,[1] but the dehydration of the intermediate exhibits unusual acidity dependence.

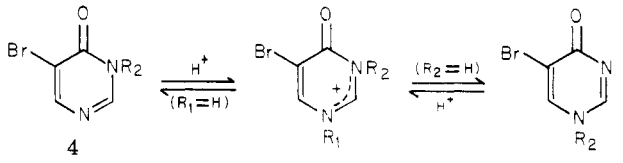
## Results and Discussion

In the vapor phase,[4] in ethanol,[4] and in aqueous solution[5] 4-hydroxypyrimidine exists mainly as the tautomer 4-(3*H*)-pyrimidinone (**1**, $R_2$ = H) and to a lesser extent as 4(1*H*)-pyrimidinone (**2**, $R_1$ = H). We have studied the




bromination of this tautomeric system, as well as of the derivatives 3-methyl-4-pyrimidinone (**1**, $R_2$ = Me) and 1-methyl-4-pyrimidinone (**2**, $R_1$ = Me) to serve as models of the principal tautomers. In addition we also studied the bromination of the 1,4-dihydro-1,3-dimethyl-4-oxopyrimidinium cation (**3**, $R_1 = R_2$ = Me) to provide a model for the protonated forms[6] of the above compounds.

All four substrates react readily with bromine in aqueous solution and give the corresponding 5-bromo derivatives (**4**, **5**, **6**), although for synthetic purposes it is more convenient to use methanol as solvent (see Experimental Section).




**Titration Studies.** The long wavelength UV absorption of 4(3*H*)-pyrimidinone (**1**, $R_2$ = H) in aqueous solution decreases rapidly upon the addition of bromine. Two mole equivalents of the halogen are required for the complete elimination of all spectral absorptions above 210 nm. In acidic media (0.05–0.5 M sulfuric accid) the reaction is perceptibly slower, and it is more apparent that the decrease in absorbance is accompanied by a bathochromic shift. Measurement of differential spectra of reaction mixtures using a reference cell containing a solution of the parent compound **1** ($R_2$ = H) shows that the bathochromic shift is due to the formation of the 5-bromo derivative **4** ($R_2$ = H).

In separate experiments it was ascertained that 5-bromo-4(3*H*)-pyrimidinone (**4**, $R_2$ = H) reacts with 1 equiv of bromine to give a product (or products) with negligible absorptions above 220 nm. We presume that this reaction, initially at least, produces a 5,5-dibromo derivative, whose structure is discussed more fully later.

At even higher acidity (2 M sulfuric acid) the reaction of bromine with the parent cation **3** ($R_1 = R_2$ = H) shows an absorbance decrease followed by a somewhat slower increase due to the formation of the 5-bromo cation **6** ($R_1 = R_2$ = H). Thus it appears that there is an intermediate of significant lifetime between **3** + $Br_2$ and the substitution product **6** (+ HBr).

Overall the titration studies show that **1** ($R_2$ = H) reacts with bromine to give an intermediate which yields the 5-bromo derivative **4** ($R_2$ = H). This product, in turn, can react further with bromine to yield, we presume, a 5,5-dibromo derivative. The methylated derivatives **1** ($R_2$ =

(1) (a) O. S. Tee and S. Banerjee, *J. Chem. Soc., Chem. Commun.*, 1032 (1972); (b) O. S. Tee and S. Banerjee, *Can. J. Chem.*, **52**, 451 (1974); (c) S. Banerjee, O. S. Tee, and K. D. Wood, *J. Org. Chem.*, **42**, 3670 (1977); (d) O. S. Tee, D. C. Thackray, and C. G. Berks, *Can. J. Chem.*, **56**, 2970 (1978).

(2) (a) S. Banerjee and O. S. Tee, *J. Chem. Soc., Chem. Commun.*, 535 (1974); (b) O. S. Tee and S. Banerjee, *Can. J. Chem.*, **57**, 626 (1979); (c) O. S. Tee and C. G. Berks, manuscript in preparation.

(3) O. S. Tee and G. V. Patil, *J. Org. Chem.*, **41**, 838 (1976).

(4) P. Beak, F. S. Fry, Jr., J. Lee, and F. Steele, *J. Am. Chem. Soc.*, **98**, 171 (1976).

(5) S. F. Mason, *J. Chem. Soc.*, 674 (1958).

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

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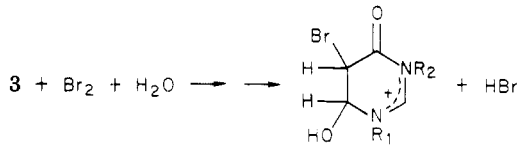
Table I. $^1$H NMR Spectral Data for Substrates 1 and 3 and Adducts 7

| structure | solvent | shifts, δ 2-H | 5-H | 6-H | $N_1$-Me | $N_3$-Me | $J_{5,6}$, Hz | $J_{5,6}$, Hz |
|---|---|---|---|---|---|---|---|---|
| 1 ($R_2$ = H) | $D_2O$ | 8.98 | 6.78 | 8.20 | | | 1.5 | 7.8 |
| 3 ($R_1$ = Me; $R_2$ = H) | 6 N DCl/$D_2O$ | 9.62 | 7.08 | 8.33 | 4.12 | | 2.0 | 7.5 |
| 3 ($R_1$ = H, $R_2$ = Me) | 6 N DCl/$D_2O$ | 9.78 | 7.05 | 8.37 | | 3.82 | 2.0 | 7.5 |
| 3 ($R_1$ = $R_2$ = Me)[a] | 4 N DCl/$D_2O$ | 9.53 | 6.86 | 8.07 | 3.99 | 3.69 | 2.3 | 7.5 |
| 7 ($R_1$ = $R_2$ = H) | 4 N DCl/$D_2O$ | 8.73 | 4.90 | 5.61 | | | | 3.6 |
| 7 ($R_1$ = Me; $R_2$ = H) | 6 N DCl/$D_2O$ | 8.98 | 5.06 | 5.68 | 3.74 | | | 3.5 |
| 7 ($R_1$ = H; $R_2$ = Me) | 6 N DCl/$D_2O$ | 9.18 | 5.19 | 5.82 | | 3.58 | | 3.6 |
| 7 ($R_1$ = $R_2$ = Me)[b] | 6 N DCl/$D_2O$ | 9.15 | 5.19 | 5.73 | 3.78 | 3.57 | | 3.5 |

[a] Introduced as the iodide or perchlorate salt. [b] Derived from 3 ($R_1$ = $R_2$ = Me) perchlorate.

Me), 2 ($R_1$ = Me), and 3 ($R_1$ = $R_2$ = Me) (perchlorate salt) behave similarly in titration with bromine, and so presumably undergo an analogous sequence of events.

**$^1$H NMR Studies.** In strong acid (4–6 N DCl/$D_2O$) the appearance of the 5-bromo cations **6** is sufficiently slow that using $^1$H NMR spectroscopy one can observe the intermediates which result from the initial reaction of the substrate cations **3** with bromine. These intermediates, which are assigned structures **7**, show spectral signals which

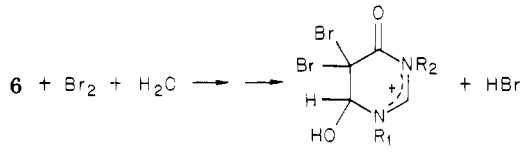



**7**

are quite distinct from those of the substrates **3** from which they are derived (see Table I).

The 5-H and 6-H of **7** appear as an AX quartet ($J \sim$ 3.5 Hz) at δ 4.9 and 5.9. When **3**-5-*d* ($R_1$ = H; $R_2$ = Me) was used as a substrate the upfield doublet (5-H) was absent, and the downfield doublet (6-H) was collapsed to a singlet. Similarly the broad singlet at δ 8.8–9.2 attributed to the 2-H of **7** was absent from spectra obtained using **3**-2-*d* ($R_1$ = H, $R_2$ = Me) as substrate. The *N*-methyl resonances of **7**, when present, appear as singlets at δ 3.6 and 3.8. In time these signals attributed to **7** are replaced by those appropriate to the 5-bromo cations **6**.

We also attempted to observe the product of the reaction of **6** with bromine, but the spectra were complex. It appears that **6** and bromine produce a product which undergoes decomposition in the acidic medium. However, by analogy with the structure of the adducts **7** we suggest that the reaction initially produces 5,5-dibromo derivatives **8**, which then undergo facile decomposition. Similar




**8**

5,5-dibromo derivatives are obtainable from 2(1*H*)-pyrimidinones,[1b,1c] from uracils,[2a,2b,7] and from 4,6-dihydroxypyrimidine (which mainly exists as 6-hydroxy-4(3*H*)-pyrimidinone).[7]

**Kinetic Studies.** We measured the acidity dependence of the rates of appearance of the various 5-bromo cations **6** arising from the dehydration of the intermediate adducts **7** generated by mixing solutions of **3** and bromine. Under conditions where the concentrations of the substrate cations **3** and of bromine are of comparable magnitude the initial bromination step (**3** → **7**) does not reach completion before appreciable dehydration (**7** → **6**) occurs, and so the appearance of **6** exhibits complex kinetic behavior. However, if the substrate **3** is present in large excess the rate of the initial step is increased relative to the rate of dehydration and the latter process exhibits good pseudo-first-order behavior if the first half-life is neglected. Pseudo-first-order rate constants ($k_{obsd}$) obtained in this way at various acidities are presented in Table II. Under the conditions outlined above the values of $k_{obsd}$ are independent of initial substrate and bromine concentrations, indicating that the formation of the adducts **7** is irreversible.

For all four reactions (**7** → **6**) the values of $k_{obsd}$ *decrease* with increasing acidity. Plots of log $k_{obsd}$ vs. the acidity

(7) S. Banerjee and O. S. Tee, *J. Org. Chem.*, **39**, 3120 (1974).

Table II. Acidity Dependence of Rates of Appearance of 6 from 7 at 30 °C

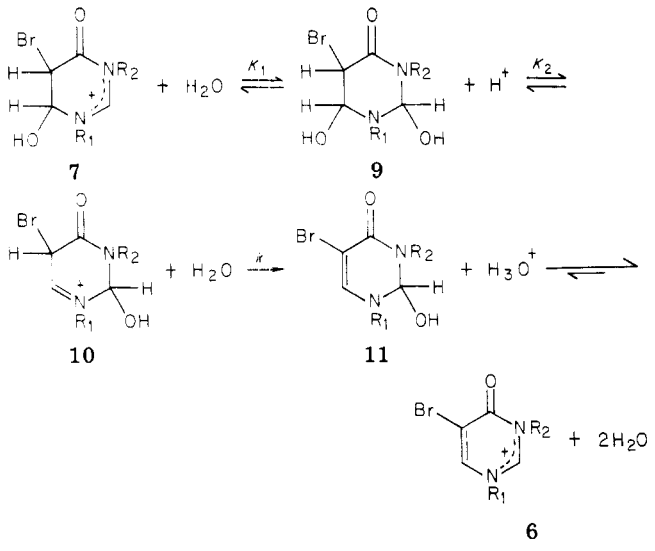
| $R_1$ | $R_2$ | $[H_2SO_4]$, M | $H_0$ | $k_{obsd} \times 10^3$, $s^{-1}$ |
|---|---|---|---|---|
| H | H | 0.50 | 0.1 | 18.7[a] |
| | | 0.60 | 0.01 | 17.0 |
| | | 1.00 | −0.30 | 13.0 |
| | | 1.20 | −0.43 | 11.7 |
| | | 1.40 | −0.55 | 10.6 |
| | | 1.60 | −0.67 | 9.42 |
| | | 1.80 | −0.78 | 8.77 |
| | | 2.00 | −0.89 | 8.03 |
| Me | H | 1.00 | −0.30 | 19.2 |
| | | 1.40 | −0.55 | 15.7 |
| | | 1.80 | −0.78 | 12.6 |
| | | 2.00 | −0.89 | 11.4 |
| | | 2.50 | −1.16 | 9.52 |
| H | Me | 1.00 | −0.30 | 27.0[b,c] |
| | | 1.40 | −0.55 | 22.8 |
| | | 1.80 | −0.78 | 17.5 |
| | | 2.00 | −0.89 | 15.7 |
| | | 2.50 | −1.16 | 11.7 |
| Me | Me[d] | 1.40 | −0.55 | 20.0 |
| | | 1.60 | −0.67 | 17.8 |
| | | 1.80 | −0.78 | 16.0 |
| | | 2.00 | −0.89 | 14.2 |
| | | 2.50 | −1.16 | 11.1[e] |

[a] Each $k_{obsd}$ is the average of four runs. [b] 5-Deuterio compound gave $k_{obsd} \times 10^3 = 17.0$ $s^{-1}$, and thus $k_H/k_D$ = 1.59. [c] Reaction in $D_2SO_4/D_2O$ gave $k_{obsd} \times 10^3 = 13.7$ $s^{-1}$, and thus $k_{H_2O}/k_{D_2O} = 1.97$. [d] Derived from 3 ($R_1$ = $R_2$ = Me) perchlorate. [e] 5-Deuterio compound gave $k_{obsd} \times 10^3 = 5.95$ $s^{-1}$, and thus $k_H/k_D = 1.87$.

Table III. Least-Squares Analysis of log $k_{obsd}$ vs. $H_0$ for 7 → 6

| $R_1$ | $R_2$ | intercept (SD) | slope (SD) | corr coeff | no. of points |
|---|---|---|---|---|---|
| H | H | −1.771 (0.002) | 0.370 (0.005) | 0.9994 | 8 |
| Me | H | −1.610 (0.004) | 0.362 (0.015) | 0.9976 | 5 |
| H | Me | −1.424 (0.007) | 0.430 (0.023) | 0.9958 | 5 |
| Me | Me | −1.468 (0.001) | 0.421 (0.007) | 0.9996 | 5 |

Scheme I



function $H_0$ show good straight lines with slopes ranging from 0.36 to 0.43 (see Table III). This behavior is unusual in that analogous dehydrations are normally acid catalyzed. For example, the rates of dehydration of the analogous intermediates involved in the bromination of 2(1*H*)-pyrimidinones[1b] and of uracils[2b] *increase* with acidity, and have slopes of log $k_{obsd}$ vs. $H_0$ of about −1. This difference in behavior originates, we believe, from the fact that in the present work the intermediates **7** undergoing dehydration are cations,[8] whereas in the literature examples cited above the intermediates are neutral.

We propose the dehydration mechanism shown in Scheme I, and attribute the inverse dependence of rate upon acidity primarily to different acidity functions governing the equilibria **7** ⇄ **9** and **9** ⇄ **10**. Assuming **9**, **10**, and **11** are only present in small amounts[9] the rate of appearance of **6** and the rate of disappearance of **7** are equal. Therefore the proposed mechanism requires

$$\text{rate} = k_{obsd}[7] = k[10]f_{10}/f_{\ddagger} \quad (1)$$

where $f_{10}$ and $f_{\ddagger}$ are the activity coefficients of **10** and the transition state of **10** → **11**, respectively. We define equilibrium constants $K_1 = [9]h_1/[7]$ and $K_2 = [9]h_2/[10]$, and acidity functions $H_1 = \log h_1$ and $H_2 = \log h_2$, which are analogous to $H_R$.[10] From these definitions and eq 1 we derive

$$k_{obsd} = \frac{k[10]f_{10}}{[7]f_{\ddagger}} = \frac{kK_1h_2f_{10}}{K_2h_1f_{\ddagger}} \quad (2)$$

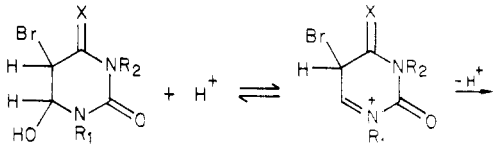
and

$$\log k_{obsd} = \log(kK_1/K_2) + H_1 - H_2 + \log(f_{10}/f_{\ddagger}) \quad (3)$$

On this basis the acidity behavior of $k_{obsd}$ depends upon the relative values of the acidity functions $H_1$ and $H_2$ and on the variation of the ratio of the activity coefficients of **10** and the transition state. At infinite dilution in aqueous solution the last three terms of eq 3 would disappear and the rate would be invariant with the acidity. However, for the media used in the present study (0.5–2.5 M $H_2SO_4$) these three terms must be considered.

We anticipate that the medium dependences of $f_{10}$ and $f_{\ddagger}$ will be very similar,[11] and thus that the difference $H_1 - H_2$ is largely responsible for the observed acidity dependence. The values of $k_{obsd}$ decrease somewhat with acid concentration and so it appears that $H_1$ is a more sensitive acidity function than is $H_2$. This is reasonable on the basis of earlier work.

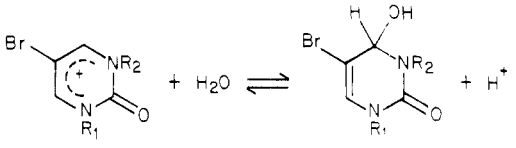
Dehydrations of the type **12** ⇄ **13** → follow acidity



**12** **13**

X = H and OH, or O; $R_1$ = $R_2$ = H or Me

functions ≃ $-1.0H_0$,[1b,2b,12] and so we expect $H_2 \simeq 1.0H_0$. The equilibrium **7** ⇄ **9** involves a fairly stable delocalized cation and so might well exhibit similar acidity behavior to the equilibrium **14** ⇄ **15**.[1c] If this is the case $H_1 \simeq$



**14** **15**

$R_1$ = $R_2$ = H or Me

$1.3H_0$, and so the differential behavior is expected to be $H_1 - H_2 \simeq 0.3H_0$. This expectation is in reasonable agreement with the observed slopes 0.36–0.43 given in Table III.

An alternative explanation of the observed behavior in relation to the proposed mechanism involves more explicit consideration of activity coefficients. In eq 2 we can make the substitutions $h_1 = a_{H^+}f_9/a_{H_2O}f_{10}$, $h_2 = a_{H^+}f_g/a_{H_2O}/f_{10}$, again by analogy with the definition of $H_R$.[10] These lead to

$$k_{obsd} = kK_1f_7/K_2f_{\ddagger} \quad (4)$$

and

$$\log k_{obsd} = \log(kK_1/K_2) + \log(f_7/f_{\ddagger}) \quad (5)$$

In this formulation the acidity behavior of $k_{obsd}$ results from differing medium dependences of the activity coefficients of the cation **7**, and of the transition state of **10** → **11**. The cation **7** is relatively stable and delocalized and so $f_7$ should vary little with increasing acid concentration.[13] On the other hand the transition state probably resembles quite closely the cation **10**, which is much less stable and more localized, and so $f_{\ddagger} \sim f_{10}$ is expected to increase significantly with acid concentration.[13] Overall, then, $k_{obsd}$ should decrease with increasing acid concentration as observed.

In an attempt to gain additional information about the mechanism of dehydration of the intermediates **7** we also measured kinetic isotope effects. Cations **7** ($R_1$ = H or Me, $R_2$ = Me) having deuterium attached at $C_5$ underwent dehydration at slower rates corresponding to isotope effects of $k_H/k_D$ = 1.59 and 1.87 (see Table II). In earlier work

(8) The chemical shifts reported in Table I are fully consistent with cationic structures for the intermediates. In particular $\delta \sim 9$ for the 2-H militates against a neutral structure. For the spectral data of related neutral structures see ref 1b, 2b, and 7.

(9) Since only **7** and **6** are observed in the $^1$H NMR experiments in acidic solutions.

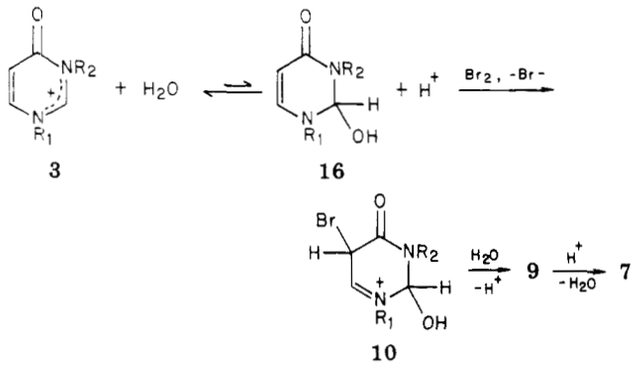
(10) E. M. Arnett and R. D. Bushick, *J. Am. Chem. Soc.*, **86**, 1564 (1964).

(11) Assuming that the transition state of **10** → **11** is quite "early" and so resembles **10**.

(12) In our earlier discussion[2b] of the dehydration of the intermediates **12** (X = O) we did not take explicit account of the activity coefficient of the deprotonation transition state. However, to the extent that this transition state is "early" and resembles **13** (X = O), the omission does not invalidate the present comparison of acidity function behavior.

(13) K. Yates and R. A. McClelland, *Prog. Phys. Org. Chem.*, **11**, 323 (1974).

**Scheme II**

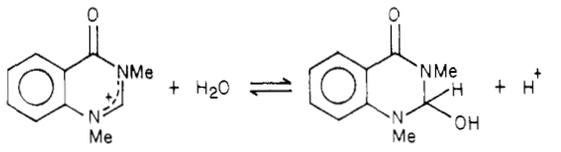


on the dehydration of intermediates involved in the bromination of 2-pyrimidinones and of uracils we found values of $k_H/k_D$ in the range 4–6.[1b,2b] The relatively low values found in the present work could result from various causes: (a) loss of deuterium due to exchange by the intermediate **7** with the solvent prior to dehydration; (b) a very early or late transition in the deprotonation step **10** → **11**; (c) the deprotonation step being only partially rate determining as a consequence of **10** → **11** and the back reaction **9** ← **10** having similar rates.

The putative cause (a) is easily eliminated in that $^1H$ NMR spectroscopic observation of the intermediates **7** in deuterated acid showed no detectable exchange prior to dehydration. In respect of (b), a late transition state for **10** → **11** does not seem likely, but an early transition state would be in keeping with the discussion of acidity dependence given above. However, we cannot rule out (c), which is exactly analogous to the situation which results in an attenuated primary isotope effect for the dehydration of the intermediate involved in the bromination of 6-methyluracil.[2b]

We also measured a solvent isotope effect of $k_{H_2O}/k_{D_2O}$ = 1.97 for the dehydration of **7** ($R_1$ = H; $R_2$ = Me) (Table II). This value is consistent with the dehydration mechanism set out in Scheme I. The effects of the deuterated medium upon the equilibrium constants $K_1$ and $K_2$ should cancel one another out;[14] in which case the observed effect results from the substitution of $D_2O$ for $H_2O$ as the base in the deprotonation step **10** → **11**. Since $D_2O$ is a weaker base than $H_2O$,[15] the substitution should result in a lower rate of reaction in $D_2O$ as observed.

**Pseudobase Studies.**[16] In other work we have provided evidence that quaternary cations derived from 2-pyrimidinone, 5-bromo-2-pyrimidinone, and 4-quinazolinone react with bromine via their pseudobases.[1c,1d,3] Therefore the facile bromination of the quaternary cation **3** ($R_1$ = $R_2$ = Me) suggested that the reaction may involve bromine attack upon the pseudobase **16** ($R_1$ = $R_2$ = Me) (Scheme II). To support this hypothesis we sought to observe **16** ($R_1$ = $R_2$ = Me) and to measure the equilibrium constant $K$ = [**16**][$H^+$]/[**3**] associated with its formation. We anticipated, however, that we might have difficulty in achieving these objectives due to lability of the pseudobase **16** ($R_1$ = $R_2$ = Me) in basic solution. From the work of others it was known that simple derivatives of **3** ($R_1$ = $R_2$ = Me) undergo irreversible ring opening and hydrolysis in alkaline media.[17] Moreover, we had previously encountered difficulties in measuring the equilibrium constant associated with the 4-quinazolinone derivatives **17** and **18**, again due to hydrolytic cleavage of the pyrimidine ring.[3]



**17** **18**

Attempts to observe the pseudobase **16** ($R_1$ = $R_2$ = Me) by $^1H$ NMR spectroscopy were unsuccessful in that the cation **3** ($R_1$ = $R_2$ = Me) underwent irreversible cleavage in dilute NaOD solutions (cf. ref 3 and 17). However, using UV spectroscopy we were able to observe the reversible formation of a new species ($\lambda_{max}$ 289 nm) from **3** ($R_1$ = $R_2$ = Me) in aqueous buffers of pH 7–9. At higher pH the 289-nm band changes irreversibly to a band around 309 nm, which in time is completely extinguished.

In potentiometric titration[18,19] the cation **3** ($R_1$ = $R_2$ = Me) behaved as an acid having p$K$ 7.27 (at 24 °C). Likewise for the 5-bromo cation **6** ($R_1$ = $R_2$ = Me) we found p$K$ 5.88. In view of the difficulties encountered in potentiometric titration of the 4-quinazolinone cation **17**,[3] we decided to confirm the p$K$ value for **3** using the UV spectrophotometric method.[18] From absorbance measurements in buffers in the pH range 6.74–8.60 we obtained p$K$ 7.53 (at 30 °C).

Assignment of $\lambda_{max}$ 289 nm (log $\epsilon$ 3.96) to the pseudobase **16** ($R_1$ = $R_2$ = Me) is supported by similarity to the values of related structures. Various compounds of the general form $Me_2NCH{=}CHCOR$ (R = H, Me, OMe, OEt) have $\lambda_{max}$ values in the region 270–300 nm.[20] More particularly the acrylamide derivative *i*-PrNHCH=CHCONMe$_2$ has $\lambda_{max}$ 283.5 nm (log $\epsilon$ 4.31).[20]

Thus it appears that the dimethyl cation **3** ($R_1$ = $R_2$ = Me) does indeed form a pseudobase **16** ($R_1$ = $R_2$ = Me) in aqueous solution, albeit unstable at higher pH. Moreover, it is reasonable that the bromination of the cation occurs by way of electrophilic attack upon the pseudobase. Earlier it was noted that the initial bromine attack is slower in more acidic media. This observation militates against direct bromine attack upon the quaternary cation, but is consistent with attack upon its pseudobase since the equilibrium concentration of this species diminishes with increasing acidity.

Assuming that the cation **3** ($R_1$ = $R_2$ = Me) reacts with bromine via its pseudobase **16** ($R_1$ = $R_2$ = Me) it is reasonable to propose that the substrates **1** ($R_2$ = H or Me) and **2** ($R_1$ = H or Me), in equilibrium with their cations **3**, react with bromine as their covalent hydrates **16** ($R_1$ or $R_2$ = H).

## Conclusions

Bromination of the 4-pyrimidinone derivatives **1** ($R_2$ = H or Me), **2** (R = H or Me), and **3** ($R_1$ = $R_2$ = Me) in aqueous acid involves a multistep addition–elimination mechanism. Initial bromine attack, probably upon the covalent hydrates or pseudobase **16**, leads to the formation of observable intermediates **7** (Scheme II). These intermediates, being cationic, exhibit unusual acidity dependence during dehydration to the 5-bromo product cations **6** (Scheme I).

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(15) This is the natural corollary of the oft stated "$D_3O^+$ is a stronger acid than $H_3O^+$".[14]
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Table IV. UV Spectral Data and Ionization Constants of the Substrates and Their Bromination Products in Aqueous Acidic Solution

| compd | p$K$ | pH or $H_0$ | $\lambda_{max}$, nm (log $\epsilon$) | ref |
|---|---|---|---|---|
| **3** ($R_1 = R_2 = H$) | 1.69 | −1.0 | 224 (3.69), 251 (3.47) | 6 |
| **3** ($R_1$ = Me; $R_2$ = H) | 2.02 | 0.0 | 229 (4.01), 252 (3.42) | 5,6 |
| **3** ($R_1$ = H; $R_2$ = Me) | 1.84 | −0.4 | 226 (3.96), 258 (3.47) | 6 |
| **3** ($R_1 = R_2$ = Me)[a] | 7.53 | 0.29 | 231 (4.06), 262 (3.47) | this work |
| **16** ($R_1 = R_2$ = Me) | | >8.6 | 289 (3.96)[b] | this work |
| **6** ($R_1 = R_2 = H$) | 0.43 | −2.4 | 241 (3.80), 273 (3.73) | 26a |
| **6** ($R_1$ = Me, $R_2$ = H) | | 0.29 | 246 (3.91), 269 (3.78) | this work |
| **6** ($R_1$ = H, $R_2$ = Me) | 0.14 | −2.0 | 246 (3.71), 277 (3.78) | 26a |
| **6** ($R_1 = R_2$ = Me)[a] | | 0.29 | 245 (3.84), 277 (3.72) | this work |

[a] Introduced as the perchlorate salt. [b] Obtained by extrapolation. See Experimental Section.

The mechanistic features of the elimination **7** ⟶ **6**, set out in Scheme I, are strongly supported by kinetic studies and by the observation of isotope effects. Confirmation that the initial states of the reaction, leading to the formation of the intermediates **7**, are as proposed in Scheme II requires a stopped-flow kinetic study. Such a study is in progress.[21]

## Experimental Section

The melting points given below are uncorrected. UV measurements were recorded on a Cary 14 instrument and an Aminco DW-2 instrument. UV spectra data and p$K$ values for the 4-pyrimidinone substrates and for their bromination products in aqueous acid are given in Table IV. $^1$H NMR spectral data for the substrates and for the unstable intermediates **7** were obtained on a Varian A-60A spectrometer (see Table I). Elemental analyses were performed by Galbraith Labs. Inc., Knoxville, Tenn.

The following compounds were prepared by literature methods: 4(3*H*)-pyrimidinone[22] (**1**, $R_2$ = H), 1-methyl-4-pyrimidinone[23] (**2**, $R_1$ = Me), and 3-methyl-4-pyrimidinone[23] (**1**, $R_2$ = Me).

**1,4-Dihydro-1,3-dimethyl-4-oxopyrimidinium (3, $R_1 = R_2$ = Me) iodide** was prepared by a method which gives much better yields than literature methods.[6,24]

4(3*H*)-Pyrimidinone (1.40 g, 14.6 mmol) and methyl iodide (10.65 g, 75 mmol) were heated together in a sealed tube at 100 °C for 13 h. Excess methyl iodide was removed under reduced pressure to give a yellow solid which upon recrystallization from ethanol gave 2.7 g (73%) of tan colored needles, mp 210.5–211.5 °C (lit.[6,24] 204–210, 205–206 °C). $^1$H NMR ($D_2O$) agreed with literature values[24] (see also Table I).

The corresponding *perchlorate* salt was made by stirring the above iodide (0.5 g, 2 mmol) with silver perchlorate (0.42 g, 2 mmol) in 10 mL of water for 30 min. Silver iodide was filtered off and evaporation of the filtrate gave a yellow product which was recrystallized from methanol to give 0.29 g (65%) of fine white needles: mp 133–134 °C; $^1$H NMR ($D_2O$) identical with that of the iodide[24] (see also Table I).

The **5-deuterio-1,4-dihydro-1,3-dimethyl-4-oxopyridinium iodide** was prepared by heating the above iodide (0.5 g, 2 mmol) in 4 mL of 2 N DCl/$D_2O$ at 100 °C for 27 h (cf. ref 24). Solvent removal and recrystallization from ethanol gave 0.4 g (80%) of the deuterated material. This was converted to the *perchlorate* salt in the manner just described and a yield of 75%. $^1$H NMR ($D_2O$) showed no trace of 5-H.

**5-Deuterio-3-methyl-4-pyrimidinone (1-*5-d*, $R_2$ = Me).** **1** ($R_2$ = Me) (0.55 g, 5 mmol) was heated in 2 N DCl/$D_2O$ at 80 °C for 40 h (cf. ref 24). Solvent removal gave a red oil which was dissolved in hot benzene and filtered through Norite. Evaporation of the benzene yielded a pale yellow material which was sublimed at 90 °C (5 mm) to give 0.29 g (52%) of deuterated product: mp 133–135 °C; $^1$H NMR ($D_2O$) indicated 92% D as position 5, and 63% D at position 2.

**2-Deuterio-3-methyl-4-pyrimidinone (1-*2-d*, $R_2$ = Me).** **1** ($R_2$ = Me) (0.55 g, 5 mmol) was heated in 5 mL of $D_2O$ at 80 °C for 15 h (cf. ref 24). Solvent removal and azeotropic distillation with benzene gave a white material which was recrystallized from benzene to yield 0.44 g (79%) of labeled product: $^1$H NMR ($D_2O$) showed <5% H at position 2.

The **5-bromo derivatives** used in this study were all made by reacting equimolar quantities of substrate (**1**, **2**, or **3**) and bromine in methanol. Solvent removal and recrystallization gave the following compounds.

**5-Bromo-4(3*H*)-pyrimidinone (4, $R_2$ = H)** as the hydrobromide salt (**6**, $R_1 = R_2$ = H, anion = $Br^-$): yield 57%; mp (EtOH) 239–241 °C dec (lit.[25] 243–246 °C dec, 252–255 °C dec); $^1$H NMR ($D_2O$/DSS) $\delta$ 8.80 (d, 1), 9.34 (d, 1), $J_{2,6}$ = 1.0 Hz.

**5-Bromo-3-methyl-4-pyrimidinone (4, $R_2$ = Me)**: yield 62%; mp (EtOH–ligroin) 152–155 °C (lit.[26] 158–159 °C); $^1$H NMR ($CDCl_3$/$Me_4Si$) agreed with literature values.[26]

**5-Bromo-1-methyl-4-pyrimidinone (5, $R_1$ = Me)** as the hydrobromide salt (**6**, $R_1$ = Me, $R_2$ = H, anion = $Br^-$): yield 40%; mp ($H_2O$) 243–244 °C dec; $^1$H NMR ($D_2O$/DSS) $\delta$ 3.85 (s, 3), 8.38 (d, 1), 8.70 (d, 1), $J_{2,6}$ = 2.2 Hz; UV in Table IV.

Anal. Calcd for $C_5H_6Br_2N_2O$: 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-1,4-dihydro-1,3-dimethyl-4-oxopyrimidium (6, $R_1 = R_2$ = Me) perchlorate**: yield 72%, mp (EtOH) darkens >220 °C, changing to semisolid, melts 260–270 °C dec; $^1$H NMR ($D_2O$/DSS) $\delta$ 3.77 (s, 3), 4.02 (s, 3), 8.72 (br s, 1), 9.75 (br s, 1); UV in Table IV.

Anal. Calcd for $C_6H_8BrClN_2O_5$: C, 23.75; H, 2.66; N, 9.23; Br, 26.33. Found: C, 23.75; H, 2.60; N, 9.17; Br, 26.49.

**Kinetic Procedures.** These were similar to those of earlier work.[1b,2b] The acid solutions and the interpolation of acidity function data were as previously.[2b] The kinetics of appearance of product cations **6** was monitored in the region 290–300 nm, the cell compartment being thermostated at 30.00 ± 0.02 °C. Absorbance data for the first half-life was ignored to allow for completion of the initial stages of the reaction which form the intermediates **7** (see text).

**Pseudobase Studies.**[16] Determination of the p$K$ by potentiometric titration[18] was carried out as in other studies.[19] To determine the p$K$ by spectrophotometry[18] UV absorbances ($A$) at 289 nm were measured for $4.0 \times 10^{-5}$ M solutions of **3** ($R_1 = R_2$ = Me) iodide in 11 buffers[27] in the pH range 6.74–8.60. Since the pseudobase **16** ($R_1 = R_2$ = Me) ($\lambda_{max}$ 289 nm) is not stable at pH 9 or above, its maximum absorbance ($A_p$) was found by least-squares fitting of eq 6 to the absorbance data. In eq 6

$$[H^+](A_c - A) = KA - KA_p \quad (6)$$

$K$ is the pseudobase formation constant and $A_c$ is the absorbance of the cation **3** ($R_1 = R_2$ = Me) at 289 nm in 0.1 M HCl. From the least-squares slope and intercept we obtained $K = 2.90 \times 10^{-8}$ M (p$K$ 7.54) and $A_p$ = 0.3618. Using this latter value, which corresponds to a molar extinction coefficient $\epsilon$ 9045 (log $\epsilon$ 3.96), in a conventional calculation[18] yielded p$K$ 7.53. Coincidently, Fife et al. have recently used this same approach to determine the p$K$ of an unstable imidazoylbenzoate ester.[28]

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**Registry No.** 1 ($R_2$ = H), 4562-27-0; 1 ($R_2$ = Me), 6104-45-6; 3 ($R_1$ = $R_2$ = H), 33612-61-2; 3 ($R_1$ = Me; $R_2$ = H), 70850-63-4; 3 ($R_1$ = H; $R_2$ = Me), 70850-64-5; 3 ($R_1$ = $R_2$ =Me) iodide, 14027-62-4; 3 ($R_1$ = $R_2$ = Me) perchlorate, 70850-65-6; 4 ($R_2$ = H), 19808-30-1; 4 ($R_2$ = Me), 14248-02-3; 5 ($R_1$ = Me), 70850-66-7; 6 ($R_1$ = $R_2$ = H) bromide, 70850-67-8; 6 ($R_1$ = Me; $R_2$ = H) bromide, 70850-68-9; 6 ($R_1$ = H; $R_2$ = Me), 70850-69-0; 6 ($R_1$ = $R_2$ = Me) perchlorate, 70850-71-4; 7 ($R_1$ = $R_2$ = H), 70850-72-5; 7 ($R_1$ = Me; $R_2$ = H), 70850-73-6; 7 ($R_1$ = H; $R_2$ = Me), 70850-73-6; 7 ($R_1$ = $R_2$ = Me), 70850-74-7; 16 ($R_1$ = $R_2$ = Me), 70850-75-8; 5-deuterio-1,4-dihydro-1,3-dimethyl-4-oxopyridinium iodide, 70850-76-9; 5-deuterio-1,4-dihydro-1,3-dimethyl-4-oxopyridinium perchlorate, 70850-78-1; 5-deuterio-3-methyl-4-pyrimidinone, 70850-79-2; 2-deuterio-3-methyl-4-pyrimidinone, 18542-92-2.

# 6,7-Dihydrocyclobuta[*g*]quinoline[1]

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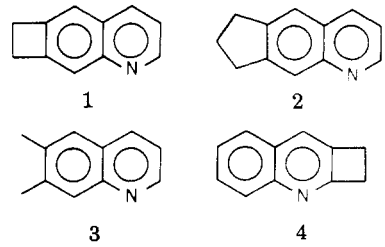
6,7-Dihydrocyclobuta[*g*]quinoline (**1**) was prepared by Skraup cyclization of 4-aminobenzocyclobutene. Similar reactions of 5-aminoindan and 3,4-dimethylaniline afforded as the major product 7,8-dihydro-6*H*-cyclopenta[*g*]quinoline (**2**) and 6,7-dimethylquinoline (**3**), respectively. Basicities of **1**–**3** and 1,2-dihydrocyclobuta[*b*]quinoline (**4**) were determined by potentiometric titration and the following p$K_a$ values were deduced: **1**, 5.45; **2**, 5.54; **3**, 5.41; **4**, 3.99. The four-membered ring in **1** caused no reduction in basicity comparable to that observed with **4**. These data are consistent with orbital rehybridization induced by ring strain, an effect which is transmitted through the $\sigma$ framework.

Twelve years ago the preparation and basicity of 1,2-dihydrocyclobuta[*b*]quinoline were reported, and it was established that the fusion of a small ring at the 2,3 position of an aza aromatic compound markedly decreased the basicity of such a strained heterocyclic system.[3] This effect, observed also with other quinoline,[4] quinoxaline,[5] and naphthyridine[6] systems, has been interpreted in terms of orbital hybridization concepts developed by Streitwieser and co-workers for strained carbocyclic compounds.[7] The smaller the fused cycloalkane moiety, the more pronounced is the effect on basicity. Although the initial report involved a fused four-membered ring,[3a] subsequent work demonstrated that five-membered rings exert a similar influence.[4-6] Heteroatoms can be incorporated into the strained ring, as shown by the extensive studies of derivatives of furo[2,3-*b*]pyridine and pyrano[2,3-*b*]pyridine.[8] Most recently, in an elegant series of papers by Thummel and Kohli, the same correlation between increased ring strain and decreased basicity was observed in a variety of mono- and bisannelated pyridines.[9-11]

The utility of the heteroaromatic systems lies in the lone pair of electrons on nitrogen which serves (under equilibrium conditions of potentiometric titration) as a probe for the strain introduced by the adjacent ring. In all of the cases cited above the nonbonded pair of electrons on N occupies a nominal $sp^2$ hybrid orbital which, as a result of increased s character, renders the electron pair less available as a Brønsted base. The nonbonding pair, therefore, is isoelectronic with the aryl carbanions generated by base-catalyzed proton abstraction from carbon-1 of biphenylene[7] and carbon-3 of benzocyclobutene.[12] Orbital rehybridization was postulated to account for the increased kinetic acidity of aryl hydrogens at sites adjacent to the junction of strained rings. Since this interpretation posits a redistribution of the fraction of s and p character in the three hybrid orbitals of a bridgehead carbon, the impact of such rehybridization is transmitted by the $\sigma$ framework of a molecule. As a consequence, the effect should be attenuated by an increase in the number of $\sigma$ bonds between the strained ring junction and the site of reactivity. Such a relationship was observed between positions 1 and 2 of biphenylene.[7] At the inception of the present work there had been no report of the dependence of heterocyclic basicity on the position of a strained ring. The recent work on cyclobuta[*b*]- and cyclobuta[*c*]-pyridines has provided the first example in a heterocyclic system.[10]

The compounds chosen for our study were 6,7-dihydrocyclobuta[*g*]quinoline (**1**), 7,8-dihydro-6*H*-cyclopenta[*g*]quinoline (**2**), and 6,7-dimethylquinoline (**3**). The



**1** **2**



**3** **4**

series was suitable for basicity comparisons with the previously reported 1,2-dihydrocyclobuta[*b*]quinoline (**4**).[3]

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