Bromide Ion Induced Debromination of the 5,5-Dibromo Derivatives of "4,6-Dihydroxypyrimidine" and 6-Methyluracil

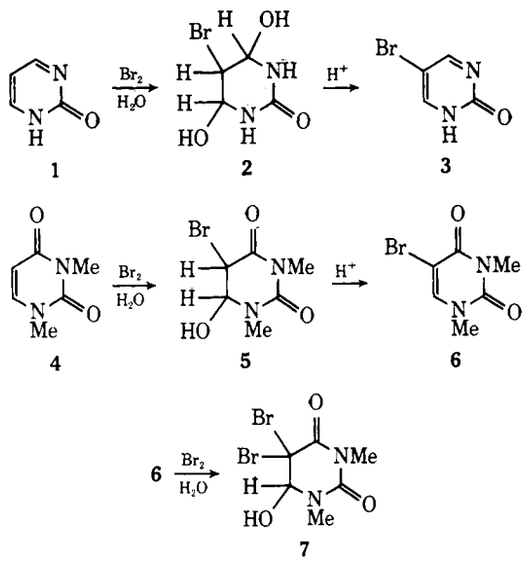
Sujit Banerjee and Oswald S. Tee*

Department of Chemistry, Sir George Williams University, Montreal H3G 1M8, Quebec, Canada

Received February 1, 1974

In aqueous solutions "4,6-dihydroxypyrimidine" and 6-methyluracil undergo rapid reaction with 2 molar equiv of bromine, to yield firstly their corresponding 5-bromo compounds, and secondly their 5,5-dibromo derivatives. Under acidic conditions, these latter compounds are acted upon by bromide ion to yield their monobromo derivatives and bromine. The liberated bromine is consumed in the presence of unreacted substrate to give a second equivalent of the 5-bromopyrimidinedione. The kinetics of debromination have been measured, and probable mechanisms for these processes are discussed with reference to previous studies on the dehalogenation of similar derivatives.

In an earlier study[1] we concluded that in aqueous sulfuric acid solutions the bromination at the 5 position of 2-pyrimidinone (1) proceeds by an addition–elimination mechanism **1** → **2** → **3**, in which acid-catalyzed deprotonation of the 5 position of **2** is the rate-determining step.[1] Similar mechanisms appear to be operative in the bromination of other pyrimidines bearing oxo and/or amino substituents at the 2 and/or 4 positions.[2] For example, 1,3-dimethyluracil (**4**) adds "HOBr" to yield the adduct **5**,[2-4] which subsequently rearomatizes to the 5-bromouracil **6** by a slow acid-catalyzed dehydration.[2] In the presence of bromine 5-bromo-1,3-dimethyluracil (**6**) forms the 5,5-dibromo derivative **7**.

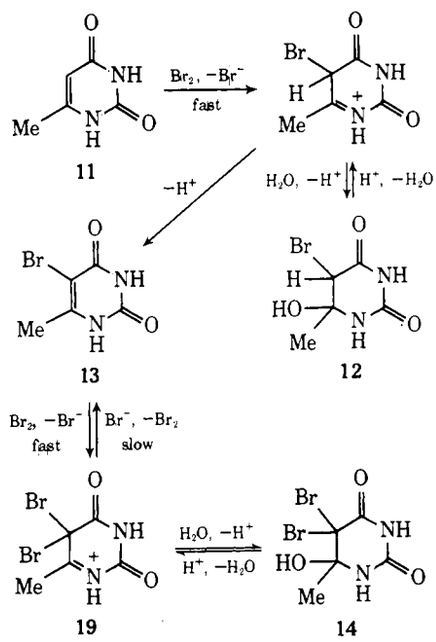


We now find that, in an analogous manner, 6-methyluracil (**11**) reacts rapidly with bromine to give, successively, **12**, **13**, and **14** (Scheme I).[5] Similarly, the reaction of "4,6-dihydroxypyrimidine" (**8**) with bromine yields a 5,5-dibromo derivative **10** *via* the 5-bromopyrimidine **9** (see Scheme II). We attempted to follow the kinetics of the brominations **8** → **9** → **10**, but obtained curious results. Subsequent experimentation revealed that these processes occur very rapidly, and that in fact the reaction we were following was the reverse reaction **10** → **9**. Similar behavior was exhibited by 6-methyluracil (**11**), and in this paper we report a kinetic study of the debrominations **10** → **9** and **14** → **13**.

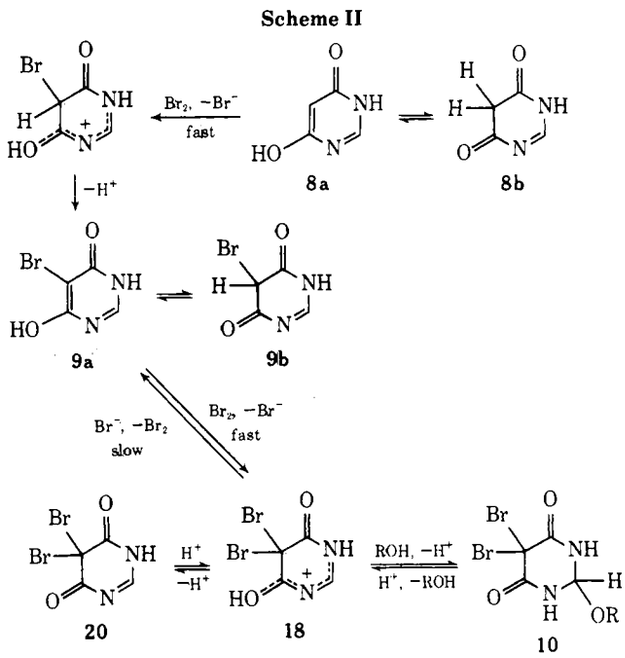
Results and Discussion

Although the major tautomeric component of "4,6-dihydroxypyrimidine" (**8**) in aqueous solutions is not known with certainty,[6] a pmr study in DMSO-d_6/D_2O solutions

Scheme I



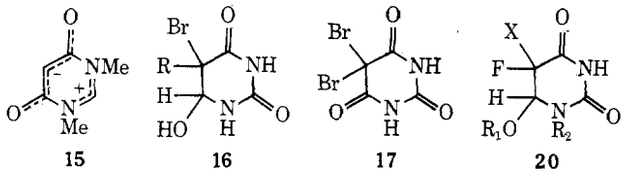
Scheme II



suggested that it exists predominantly in the enol–oxo form **8a**, with a small contribution from the dioxo form **8b**.[7] 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.[7] Similar isotopic exchange occurs with the betaine **15** in acidic D_2O solutions.[8]

Since the acid-catalyzed exchange at the 5 position of **8** occurs more easily than that of 2-pyrimidinone (**1**)[9] or 1,3-dimethyluracil (**4**),[10] it might be anticipated that the analogous bromination of **8** would also be faster than that of **1** or **4**. Upon addition of 2 molar equiv of bromine to a solution of "4,6-dihydroxypyrimidine" (**8**) in aqueous sulfuric acid,[11] the uv absorption appropriate to **8** (λ_{max} 253 nm)[12] is removed, and the resulting solution has λ_{max} below 210 nm, with a significant tail end absorption extending beyond 240 nm. With stepwise addition of bromine, the decrease in absorbance due to **8** is accompanied by shifts to longer wavelengths, suggesting the intermediate formation of the 5-bromo derivative **9** which has λ_{max} at 261 nm. Spectrophotometric titration of **9** with bromine shows that 1 molar equiv of bromine is required for complete reaction, with isosbestic points being obtained at 215 and 240 nm. 6-Methyluracil (**11**) behaves similarly on titration with bromine, in that 2 molar equiv of bromine is required for complete removal of the absorption maximum at 261 nm,[13] and the absorbance decrease is accompanied by bathochromic shifts. Furthermore, the 5-bromo derivative **13** reacts smoothly with 1 molar equiv of bromine, as suggested by the elimination of its maximum at 276 nm and the presence of an isosbestic point at 211 nm.

Under synthetic conditions, **8** reacts with equivalent quantities of bromine in water,[14] acetic acid,[14] or methanol to give 5-bromo-"4,6-dihydroxypyrimidine" (**9**). Addition of 2 molar equiv of bromine to a methanolic suspension of **8** yields the 5,5-dibromo derivative **10** (R = Me). Attempts to isolate a similar dibromo derivative **10** (R = H) from water failed, the reaction being accompanied by extensive evolution of carbon dioxide.[15] However, pmr spectra of solutions obtained by the addition of excess bromine to a D_2O suspension of **8** or **9** show a signal at δ 6.08 attributable to the 2-H of **10** (R = H). This signal gradually decays with the appearance of other signals which are attributed to decomposition products.[15] Similar spectra were obtained on treatment of the monobromo derivative **9** with bromine. These observations, and the spectrophotometric titration data, suggest the rapid formation of the 5,5-dibromo derivative **10** (R = H). The compound **10** (R = Me) liberates iodine from solutions of potassium iodide, and in the presence of bromide ion and acid it converts **8** to the monobromopyrimidine **9**, during the course of which **10** itself is also converted to **9**. The reactivity of 5,5-dibromopyrimidine derivatives is well established, as illustrated by the facile debromination of the uracil adduct **16** (R = Br), the thymine adduct **16** (R = Me), and 5,5-dibromobarbituric acid (**17**).[17] Recently we have found that similar reversals occur from monobromo adducts of the type **16** (R = H), as well as those obtained from other oxo- and aminopyrimidines.[2]



15 **16** **17** **20**

Treatment of 6-methyluracil (**11**) with 2 molar equiv of bromine leads to the adduct **14**. The behavior of **14** toward halide ions is similar to that exhibited by **10**, to the extent that it liberates iodine from solutions of potassium iodide, and in the presence of bromide ion and acid it converts **11** to **13**, and is itself converted to **13**.

Table I
Variation of the Rate of Appearance of 5-Bromo-"4,6-dihydroxypyrimidine" (9) with [Br^-] in 1.00 N H_2SO_4[a,b]

[Br^-][c] × 10^4, M	[KBr] × 10^4, M	Total [Br^-] × 10^4, M	k_{obsd} × 10^5, sec^{-1}
2.55		2.55	7.43
2.91		2.91	8.81
3.52		3.52	10.1
5.06		5.06	14.0
5.56		5.56	14.5
5.65		5.65	15.8
5.88		5.88	15.6
6.61		6.61	17.7
6.73		6.73	16.9
8.37		8.37	20.9
8.61		8.61	22.1
10.8		10.8	27.1
11.2		11.2	28.8
12.3		12.3	28.4
16.4		16.4	36.9
5.71	4.91	10.6	26.2
4.83	10.3	15.2	35.2
5.26	13.6	18.9	41.9
4.62	19.7	24.3	54.9
4.87	20.9	25.8	59.3
4.53	27.3	31.8	69.9
4.43	28.3	32.7	67.0

[a] At this acidity, [H_3O^+] = 0.511 M (ref 1). [b] [8] = 1.5 × 10^{-3} to 6.0 × 10^{-3} M. [c] Derived from initial bromine concentration.

The reaction of 6-methyluracil (**11**) and "4,6-dihydroxypyrimidine" (**8**) with bromine thus appears to involve rapid formation of the monobromo derivatives, which in turn also react rapidly with bromine to give the corresponding 5,5-dibromopyrimidine derivatives. These subsequently react with substrate to yield the monobromo products. The kinetics of the latter processes were measured spectrophotometrically by monitoring the appearance of 5-bromo products at fixed wavelengths. The initial bromination steps were found to be too fast to be followed by conventional spectrophotometric methods.

Under conditions where the concentrations of **8** and bromine are comparable, complex kinetic behavior is encountered. However, linear first-order plots are obtained when the concentration of **8** exceeds that of bromine by a factor of 4 or more. First-order rate constants obtained in 1.00 N sulfuric acid solutions are independent of substrate concentration, but appear to be linearly dependent on bromine. Since the reaction of **8** with bromine is rapid in comparison to the rate of appearance of **9**, this apparent dependence on bromine may be interpreted as arising from the bromide ion formed in the reaction sequence **8** → **9** → **10**. This was confirmed by experiments in which bromine was added to mixtures of potassium bromide and **8** in solution, where plots of log k_{obsd} *vs.* ([KBr] + initial [Br_2]) yielded the same second-order rate constant (19.8 ± 1.04 M^{-1} sec^{-1}) as that obtained in the absence of potassium bromide (21.6 ± 0.6 M^{-1} sec^{-1}). Kinetic data for these processes are summarized in Table I, those for other acidities being listed in Table II and plotted against bromide ion concentration in Figure 1.

Table II[a]
Variation of the Rate of Appearance of 5-Bromo-"4,6-dihydroxypyrimidine" (9) with $[Br^-]$[b] and $[H_3O^+]$

$[H_2SO_4]$, N	0.100		0.300		0.500		0.700	
$[H_3O^+]$, M	0.059		0.160		0.261		0.361	
	$[Br^-] \times 10^4$, M	$k \times 10^3$, sec^{-1}	$[Br^-] \times 10^4$, M	$k \times 10^3$, sec^{-1}	$[Br^-] \times 10^4$, M	$k \times 10^3$, sec^{-1}	$[Br^-] \times 10^4$, M	$k \times 10^3$, sec^{-1}
	4.51	2.21	6.25	5.63	3.40	5.30	4.96	8.72
	4.84	2.37	7.18	6.60	5.68	7.81	6.16	11.1
	5.74	2.52	9.14	7.65	5.96	8.79	8.04	13.5
	8.61	3.10	13.7	9.27	6.48	8.35	9.47	15.0
	9.19	3.34	13.7	10.4	10.8	13.4	11.8	18.4
	11.0	3.63	17.5	11.4	11.4	13.3	15.3	22.7

[a] These data, together with part of that from Table I, are plotted in Figure 1. [b] Derived from initial bromine concentration.

Table III[a]
Variation of the Second-Order Rate Constant k for the Appearance of 5-Bromo-"4,6-dihydroxypyrimidine" (9) with $[H_3O^+]$

$[H_2SO_4]$, N	$[H_3O^+]$, M	k, M^{-1} sec^{-1}
0.100	0.059	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[b]

[a] Plotted in Figure 2. [b] Rates were measured in the presence of KBr.

Second-order rate constants which include the bromide ion catalytic coefficient are linearly dependent on acidity. These values are summarized in Table III and plotted in Figure 2. Thus, the conversion of **10** to the 5-bromo derivative **9** seems to be subject to catalysis by bromide ion[18] as well as by hydronium ion.[19] A small contribution from a water reaction on **10** (R = H) is also suggested by the nonzero intercepts in Figure 1.

Kinetics were also measured for the reaction of the isolable dibromo derivative **10** (R = Me) with **8** in acidic solutions and in the presence of bromide ion, as well as for the reaction of **10** (R = H) (generated by the addition of bromine to the 5-bromo compound **9**) with **8**. In all cases the rate constants obtained were identical within experimental error with those listed in Tables I and II.

These findings may be rationalized by the sequence outlined in Scheme II, and by using the following analysis.[21]

$$8 + Br_2 \xrightarrow[\text{fast}]{k_1} 9 + H^+ + Br^- \quad (1)$$

$$9 + Br_2 \xrightarrow[\text{fast}]{k_2} 10 + H^+ + Br^- \quad (2)$$

$$10 + H^+ + Br^- \xrightarrow[\text{slow}]{k_3} 9 + Br_2 \quad (3)$$

Upon mixing of the substrate **8** and bromine there is rapid formation of both **9** and **10** (eq 1 and 2) 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 **8** and **9** does the slow back-reaction **10** → **9** (eq 3) become apparent. Moreover, since **8** is in excess, and probably $k_1 > k_2$, any bromine produced by the k_3 step is scavenged by **8** and converted to **9**. That is, during the slow later 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 **9** (and HBr), since **8** is always in excess.

At any time the rate of formation of **9** is

$$\frac{d[9]}{dt} = (k_1[8] - k_2[9])[Br_2] + k_3[10][H^+][Br^-] \quad (4)$$

and that of bromine is

$$\frac{d[Br_2]}{dt} = k_3[10][H^+][Br^-] - (k_1[8] + k_2[9])[Br_2] \quad (5)$$

During the latter stages of the reaction, bromine is present in steady-state amounts, since both of the processes (eq 1 and 2) which consume bromine are very much faster than that (eq 3) which produces it. Setting eq 5 = 0 gives

$$[Br_2] = \frac{k_3[10][H^+][Br^-]}{k_1[8] + k_2[9]}$$

and substitution into eq 4 yields

$$\frac{d[9]}{dt} = \frac{2k_1k_3[8][10][H^+][Br^-]}{k_1[8] + k_2[9]} \quad (6)$$

Under the conditions of our experiments [8] ≫ [9], and since almost certainly $k_1 > k_2$, eq 6 simplifies to

$$\frac{d[9]}{dt} = 2k_3[10][H^+][Br^-] \quad (7)$$

We believe, therefore, that the slow appearance of **9** which follows an initial rapid increase in absorbance due to **9** arises from the bromide ion induced debromination of **10** *via* **18**. This reaction (eq 3), is, of course, the microscopic reverse of the bromination of **9** (eq 2), and its rate should be dependent upon both acid and bromide ion concentration (eq 7) as observed.

If, during our experiments, **8** were not in excess with respect to initial bromine, the concentration of **9** might exceed that of **8** during the reaction and give rise to a breakdown of the inequality $k_1[8] \gg k_2[9]$. Under these particular circumstances eq 6 would give rise to more complex kinetic behavior, as we have observed.

Similar kinetic behavior was obtained for the reaction of 6-methyluracil 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 behavior 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 **14** with 6-methyluracil in acidic solutions in the presence of potassium bromide, and imply that **13** is formed from a protonated species such as **19** derived from the dibromo adduct **14**, as illustrated in Scheme I. Rate results are tabulated in Table IV, and the

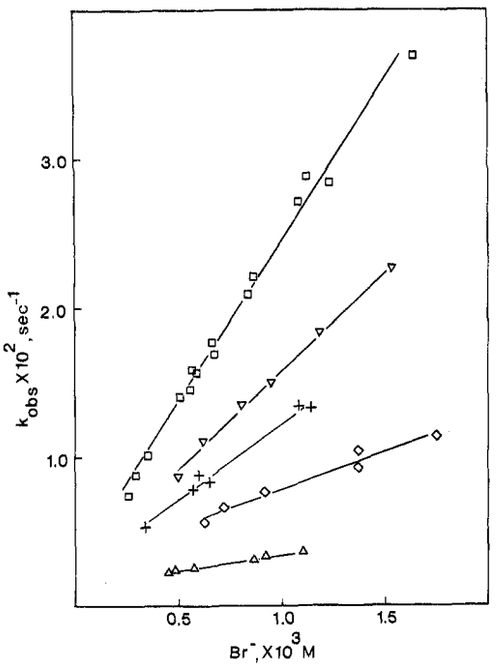


Figure 1. Variation of the rate of appearance of 5-bromo-"4,6-dihydroxypyrimidine" (9) with [Br^-] in sulfuric acid solutions of the following normalities: □= [*I*] *N*; ▽, 0.700 *N*; +, 0.500 *N*; ◇, 0.300 *N*; △, 0.100 *N*.

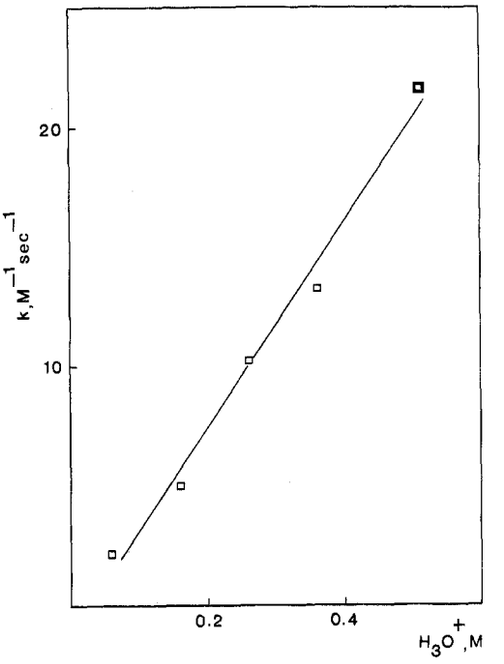


Figure 2. Variation of the second-order rate constant *k* for the appearance of 5-bromo-"4,6-dihydroxypyrimidine" (9) with [H_3O^+].

Table IV
Variation of the Rate of Appearance of 5-Bromo-6-methyluracil (13) with the Acidity Function H_0

$[H_2SO_4]$, *N*	H_0	$k_{obsd}/[Br^-]$[a] × 10^2, M^{-1} sec^{-1}	log ($k_{obsd}/[Br^-]$)
1.00	0.10	0.450	−2.3468
1.20	0.01	0.495[c]	−2.3054
2.00[b]	−0.30	1.53	−1.8163
2.80[b]	−0.55	2.33	−1.6320
3.00	−0.61	2.92[c]	−1.5351
4.00	−0.89	6.33	−1.1984
5.00[b]	−1.16	14.4	−0.8416

[a] Average of two determinations; plotted in Figure 3. [b] Rate data refer to the reaction of 14 with 11 in the presence of KBr. [c] Single determination.

dependence of log ($k_{obsd}/[Br^-]$ with the acidity function H_0 is shown in Figure 3.[22]

Analysis of the sequence

$$11 + Br_2 \xrightarrow[\text{fast}]{k_1} 13 + H^+ + Br^-$$

$$13 + Br_2 \xrightarrow[\text{fast}]{k_2} 14 + H^+ + Br^-$$

$$14 + H^+ + Br^- \xrightarrow[\text{slow}]{k_3} 13 + Br_2$$

along the lines outlined for the "4,6-dihydroxypyrimidine"–bromine reaction yields

$$\frac{d[13]}{dt} = 2k_3[14][H^+][Br^-] \quad (8)$$

for the slow appearance of 13 during the latter stages of the reaction of 11 with bromine. The derivation of eq 8 is dependent upon the validity of the inequality $k_1[11] \gg k_2[13]$. Since we observe that it is not necessary to have a large excess of 6-methyluracil (11) over bromine to obtain good pseudo-first-order kinetics, it would appear that $k_1 \gg k_2$; *i.e.*, the bromination of 6-methyluracil (11) is very much faster than that of 5-bromo-6-methyluracil (13). The correspondence between our analysis of Scheme I and our experimental observations again leads us to believe that the reaction followed was an acid-catalyzed bromide ion induced debromination, namely 14 → 13.

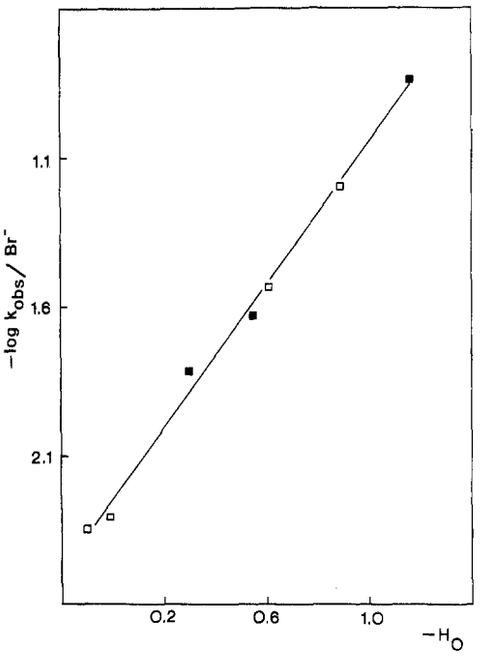
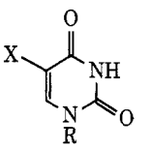


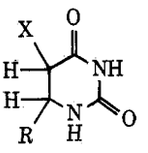
Figure 3. Variation of the rate of appearance of 5-bromo-6-methyluracil (13) with the acidity function H_0: □, from the reaction of 11 with bromine; ■, from the reaction of 14 with 11 in the presence of KBr.

Dehalogenation reactions similar to those of 10 and 14 appear to be of significance in biological processes. Dus-

chinsky, *et al.*,[23] have prepared a series of 5,6-substituted 5-fluorodihydrouracils and their corresponding 2′-deoxyribonucleosides **20** (X = Br, Cl; R_1 = H, Me, Et, *t*-Bu, etc; R_2 = H, 2′-deoxyribosyl), and have shown that a qualitative correlation exists between the stability of **20** toward reduced glutathione and its activity against mouse leukemia B82A. Such activity was presumed to arise from the release of 5-fluorouracil or 5-fluorouridine from the dihalogeno adducts **20.** Garrett, *et al.*,[24] have also observed dehalogenation processes in the hydrolysis of 5-iodouridine **21** (X = I; R = 2′-deoxyribosyl). Under acidic conditions, the nucleoside is converted to 5-iodouracil, and deiodination of the latter was postulated to occur *via* an addition–elimination mechanism involving loss of iodonium ion from the adduct **22** (X = I; R = OH). More recently it has been shown that the 5-halouracils **21** (X = Cl, Br, I; R = H) dehalogenate in the presence of sodium bisulfite,[25] and it was suggested that loss of halonium ion occurs from the bisulfite adduct **22** (X = Cl, Br, I; R = OSO_2H).

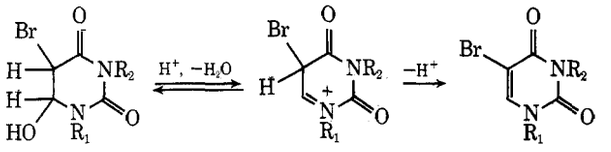


21



22

In conclusion we point out the similarities between the debromination reactions of **10** and **14** and the dehydration process **23** → **25.** For the latter, measured isotope effects[2]



23 **24** **25**

R_1 = H, Me; R_2 = H, Me

suggest that the cleavage of the C_5–H bond (**24** → **25**) is rate determining. Therefore, again consistent with the kinetic results presented above, one would expect the breaking of the C_5–Br bonds of **18** (Scheme II) and **19** (Scheme I) to be the rate-determining steps in the conversion of **10** → **9** and **14** → **13**, respectively.

Experimental Section

The melting points given below are uncorrected. Uv measurements were made on a Cary 14 instrument, pmr spectra were obtained from a Varian A-60 spectrometer, and the mass spectrum[26] was run on a Perkin-Elmer Hitachi RMU-6E spectrometer. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.

"4,6-Dihydroxypyrimidine" (8) from Aldrich was recrystallized from water before use.

The following were prepared according to literature methods: **5-bromo-6-methyluracil**[27] **(13)** and **5,5-dibromo-6-hydroxy-6-methyldihydrouracil**[28] **(14).**

5-Bromo-"4,6-dihydroxypyrimidine" (9). This compound has previously been synthesized by the bromination of **8** in acetic acid[14] or warm water,[14] but it may be prepared in higher yield by bromination in methanol.

Bromine (1.6 g, 0.01 mol) in 10 ml of absolute methanol was added to a suspension of "4,6-dihydroxypyrimidine" (**8**, 1.12 g, 0.01 mol) in 10 ml of absolute methanol. Removal of methanol under reduced pressure and recrystallization of the residue from water gave 1.6 g (84%) of **9**: mp 261–263° dec (lit.[14] mp 263–264° dec); pmr (DMSO-d_6) δ 7.82 (broad s, 2), 8.50 (s, 1); uv (1.00 *N* H_2SO_4) λ_{max} (log ϵ) 204 (4.36), 261 (4.05).

5,5-Dibromo-4,6-dioxo-2-methoxyhexahydropyrimidine (10, R = Me). Bromine was added dropwise with stirring to a suspension of **8** (0.56 g, 0.005 mol) in 5 ml of absolute methanol until the color persisted. Refrigeration of the mixture and filtration afforded a pale yellow material which was found to contain some of the starting material **8.** The bromination process was repeated to give 1.23 g (82%) of the dibromo derivative **10** (R = Me) as white crystals which were recrystallized from acetone–ligroin (bp 30–60°). The compound melted at 176–178° with strong effervescence, resolidified to a yellow material which darkened above 220°, and melted with decomposition at 232–240°: pmr (DMSO-d_6) δ 3.23 (s, 3), 5.47 (t, 1), 9.76 (d, 2) (J = 3.1 Hz). Addition of D_2O led to the collapse of the low-field signals to a singlet. The mass spectrum (run at a source temperature of 170°)[26] did not show a molecular ion peak corresponding to *m/e* 302, but showed triplets of intensity ratio 1:2:1 at *m/e* 273, 271, and 269 and at 272, 270, and 268.

Anal. Calcd for $C_5H_6N_2O_3Br_2$: C, 19.89; H, 2.00; N, 9.28; Br, 52.93. Found: C, 19.97; H, 1.90; N, 9.29; Br, 52.92.

Kinetic Procedures. Sulfuric acid and sodium thiosulfate were prepared from commercial standard volumetric concentrates. Solutions of bromine in aqueous sulfuric acid were estimated by titration against sodium thiosulfate. The concentration of hydronium ion in dilute sulfuric acid was calculated as described earlier.[1] For solutions of stronger acidity, "weight per cent H_2SO_4" was converted to normality using appropriate density values,[29] and corresponding H_0 values for the latter[30] were fitted to a power series, which then allowed direct conversion of normality to H_0 for any value of normality.

Rates of product formation were measured by monitoring a suitable wavelength in the 300–340-nm region using a Cary 14 spectrophotometer. Temperature control was maintained by circulating water through the cell holders from a Neslab TE9 constant-temperature bath kept at 30.00 ± 0.02°. Solutions of substrate were pipetted directly into the cell, and the reaction was started after temperature equilibration by adding 0.1 or 0.2 ml of the reactant solution. Measurements were normally taken over at least 3 half-lives for the faster runs $t_{1/2} \leq 20$ min) and 2 half-lives for the slower runs. The rate constants reported were obtained from first-order rate plots whose correlation coefficients exceeded 0.9998 for the slower and 0.9996 for the faster runs.

Acknowledgment. The authors thank the National Research Council of Canada for financial support.

Registry No.—**8a,** 1193-24-4; **8b,** 25286-58-2; **9a,** 15726-38-2; **9b,** 52176-13-3; **10** (R = Me), 52176-14-4; **13,** 15018-56-1.

References and Notes

(1) O. S. Tee and S. Banerjee, *J. Chem. Soc., Chem. Commun.*, 1032 (1972); *Can. J. Chem.*, **52,** 451 (1974).
(2) O. S. Tee and S. Banerjee, *J. Chem. Soc., Chem. Commun.*, 535 (1974), and unpublished results.
(3) A. M. Moore and S. M. Anderson, *Can. J. Chem.*, **37,** 590 (1959).
(4) S. Y. Wang, *J. Org. Chem.*, **24,** 11 (1959).
(5) The kinetics of the dehydration reaction **12** → **13** have been studied.[2]
(6) Studies into the structure of this compound have been reviewed by M. Prystas, *Collect. Czech. Chem. Commun.*, **32,** 4241 (1967).
(7) Y. Inoue, N. Furutachi, and K. Nakanishi, *J. Org. Chem.*, **31,** 175 (1966).
(8) G. M. Kheifets, N. V. Khromov-Borisov, and A. I. Kol'tsov, *Dokl. Akad. Nauk SSSR*, **166,** 635 (1966).
(9) A. R. Katritzky, M. Kingsland, and O. S. Tee, *Chem. Commun.*, 289 (1968); *J. Chem. Soc. B*, 1226 (1968).
(10) O. S. Tee, Ph.D. Thesis, University of East Anglia, 1967.
(11) The choice of an acidic medium was made for three reasons: (a) to swamp out any effects of HBr produced during substitution; (b) to facilitate interconversion of the tautomers **8a** and **8b;** (c) for the comparison of results to our previous studies.[1,2]
(12) D. J. Brown and T. Teitei, *Aust. J. Chem.*, **17,** 567 (1964).
(13) J. R. Marshall and J. Walker, *J. Chem. Soc.*, 1004 (1951).
(14) J. Chesterfield, J. F. W. McOmie, and E. R. Sayer *J. Chem. Soc.*, 3478 (1955).
(15) Ring opening could lead to dibromomalonic acid, which readily decarboxylates.[16]
(16) E. H. Rodd, "Chemistry of Carbon Compounds," Vol. I, Elsevier, Amsterdam, 1952, Part B.
(17) D. J. Brown, "The Pyrimidines," Vol. XVI, "The Chemistry of Heterocyclic Compounds," A. Weissberger, Ed., Interscience, New York, N. Y., 1962.
(18) The presence of potassium chloride had no effect on the reaction rate.
(19) Iodide-induced dehalogenation of vicinal dibromides in polar solvents is well known.[20]
(20) A. F. Cockerill in "Comprehensive Chemical Kinetics," Vol. IX, C. H. Bamford and C. F. H. Tipper, Ed., Elsevier, Amsterdam, 1973.
(21) An equivalent analysis pertains to Scheme I.
(22) A water reaction on **14** would tend to deviate the plot toward nonlinearity. However, the magnitude of this reaction is likely to be small and is ignored.
(23) R. Duschinsky, T. Gabriel, W. Tautz, A. Nussbaum, M. Hoffer, E. Grunberg, J. H. Burchenal, and J. J. Fox, *J. Med. Chem.*, **10,** 47 (1967).

(24) E. R. Garrett, T. Suzuki, and D. J. Weber, *J. Amer. Chem. Soc.*, **86**, 4460 (1964).
(25) E. G. Sander and C. L. Deyrup, *Arch. Biochem. Biophys.*, **150**, 600 (1972).
(26) We thank Dr. R. T. B. Rye for taking the mass spectrum.
(27) R. C. Elderfield and R. N. Prasad, *J. Org. Chem.*, **25**, 1583 (1960).
(28) R. Behrend, *Justus Liebigs Ann. Chem.*, **229**, 18 (1885).
(29) "International Critical Tables," **3**, 56 (1928).
(30) C. D. Johnson, A. R. Katritzky, and S. A. Shapiro, *J. Amer. Chem. Soc.*, **91**, 6654 (1969).

Three-Membered Rings. VII. Solvent Control of the Cis–Trans Isomer Ratio in the Preparation of a Phosphonate Substituted Cyclopropane[1]

Eckhard W. Hellmuth, John A. Kaczynski, James Low, and Layton L. McCoy*

Department of Chemistry, University of Missouri—Kansas City, Kansas City, Missouri 64110

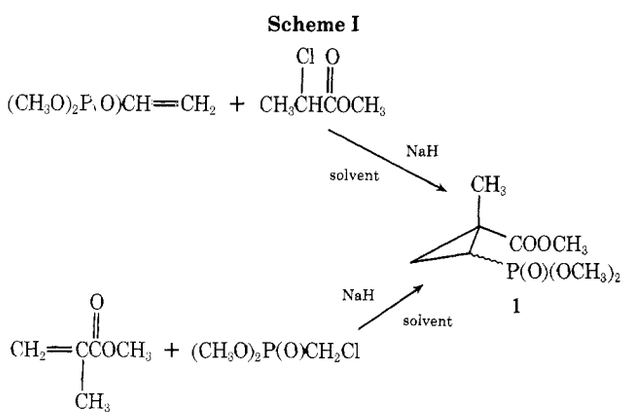
Received March 12, 1974

Dimethyl 2-methyl-2-carbomethoxycyclopropylphosphonate was prepared by the reaction of methyl methacrylate with dimethyl chloromethylphosphonate and sodium hydride in solvent mixtures varying from pure benzene through benzene–dimethylformamide to pure dimethylformamide. Two isomers were observed in all solvents. The stereochemistry proposed for them is based on analysis of their nuclear magnetic resonance spectra. The ratio of trans isomer to cis isomer was determined by gas chromatographic analysis and confirmed by nuclear magnetic resonance spectral analysis. Although log (trans isomer/cis isomer) produces a linear relationship when plotted against the Kirkwood–Onsager term, $(\epsilon - 1)/(2\epsilon + 1)$, for solvent polarity, the correlation is the inverse of nearly all such cases previously reported, *i.e.*, the cis isomer predominates in the polar solvent dimethylformamide and the trans isomer predominates in the nonpolar solvent benzene.

A general procedure for the preparation of polysubstituted cyclopropanes has been examined in earlier papers of this series[2] and in work reported by others.[3] The procedure involves treatment of an α-halo compound with an α,β-unsaturated compound in the presence of a base and solvent. All of the groups reported to "activate" the α-halogen compound and the olefinic compound might be termed carbon functional groups, *i.e.*, functional groups with a central carbon such as esters, amides, nitriles, and ketones. Cyclopropane products thus formed are at least difunctional. The functional groups, the "activating" groups, are on adjacent positions of the cyclopropane ring, oriented cis or trans. It has been observed that the cis/trans isomer ratio is dependent on the solvent: when the solvent is nonpolar, *e.g.*, benzene, the cis isomer predominates, while when the solvent is polar, *e.g.*, dimethylformamide, the cis/trans isomer ratio decreases, usually leading to a preponderance of the trans isomer.[2b] The present report gives an extension of the previous work to include a heteroatom functional group, the phosphonate moiety, and an examination of the solvent effect in this system.

The dimethyl phosphonate group was used to activate either the α-halo group or the olefinic group as shown in Scheme I.[4] Although a variety of conditions for the preparation of compound 1 were used, no systematic study to optimize the yield was attempted. Gas chromatographic analysis showed the presence of two isomers as expected. Complete separation of these isomers was not accomplished in either analytical or preparative scale gas chromatography, but separation was sufficient to determine isomer ratios (confirmed by integrated peak ratios in the nmr spectra of mixtures), to obtain the nmr spectra of each isomer, and to give enriched materials for subsequent saponification. The first isomer eluted in these separations is designated as isomer A, the second isomer B. Control experiments showed that these isomers do not interconvert under the preparative reaction conditions.

Scheme I



Preparation of compound 1 in solvents varying from *N,N*-dimethylformamide (DMF) through mixtures of DMF with benzene to benzene produced changes in the ratio isomer B/isomer A, as seen in Table I. Although these studies of the effect of solvent used the dimethyl chloromethylphosphonate pathway, the dimethyl vinylphosphonate pathway did show the same isomer preference in the nonpolar solvent benzene (the polar solvent dimethylformamide was not examined). In similar studies of isomer ratio–solvent relationships in the preparation of some cyclopro-

Table I
Solvent Composition, Kirkwood–Onsager Term Values, Yields, and Isomer Ratios for the Preparation of Dimethyl 2-Methyl-2-carbomethoxycyclopropylphosphonate

Solvent ratio HC(=O)NMe2:C6H6	$(\epsilon - 1)/(2\epsilon + 1)$	Yield of phosphonate, %	B/A (trans/cis)	Log (trans/cis)
10:0	0.4803	18	0.19	−0.72
9:1	0.4631	19	0.23	−0.64
8:2	0.4446	38	0.27	−0.57
7:3	0.4246	37	0.42	−0.38
6:4	0.4034	26	0.56	−0.25
5:5	0.3803	35	0.87	−0.06
4:6	0.3555	12	1.27	+0.10
3:7	0.3284	16	1.75	+0.24
2:8	0.2984	8	2.9	+0.46
1:9	0.2627	17	7.9	+0.90
0:10	0.2302	6	14.8	+1.17