obtained from the completely basified aqueous solution in 73% yield. Distillation afforded pure **3** without difficulty.

Isopropyl-2,2-dichloroethylamine (11).—The best preparation of **11** resulted from maintaining a very high acid/chloramine ratio as follows. A solution containing 0.07 mol of isopropylchloramine in 64 ml of concentrated H_2SO_4 and 124 ml of glacial acetic acid (6 *M* H_2SO_4) was purged at 25° with nitrogen for 15 min as usual and then treated under irradiation with gaseous vinyl chloride to completion of the reaction. The mixture was poured over 200 g of ice, diluted with 700 ml of water, extracted with pentane (no neutral products isolated), and fully basified with 295 ml of 12 *N* NaOH. The 6.6 g of crude **11** (61%) was extracted into a total of 350 ml ether and subsequently purified by an unusually efficient distillation.

Attempted Addition of N-Chlorinated 10 to 2-Chloropropene.—The crude N-chloro derivative of adduct **10** was prepared by stirring 0.05 mol of **10** and 0.05 mol of *t*-butylhypochlorite in 200 ml of ether for 60 min at room temperature. Ether was removed from N-chloro **10**, the residue was dissolved in 22 ml of concentrated H_2SO_4, and this was added to 75 ml of glacial acetic acid in the Vicor flask. Irradiation in the presence of a total 0.10 mol of 2-chloropropene for 15 min destroyed the active chlorine, but normal work-up gave 50% of **10** as the only isolable product.

Kinetics and Mechanisms of Hydrolysis of 5-Halouracils[1]

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The determined log *k*–pH profiles for the hydrolyses of the 5-fluoro-, 5-chloro-, 5-bromo-, and 5-iodouracil and their heats of activation at several pH values are similar. The ease of hydrolysis increases with the stated sequence. The observed major products of the strongly alkaline hydrolysis of 5-iodouracil are uracil and barbituric acid, whereas only the barbituric acid product is observed for 5-bromouracil. The rates of production of these products are dependent on hydroxyl ion attack on the halouracil monoanion or the kinetically equivalent solvent attack on the dianion. A certain fraction of the halouracil produces a nonchromophoric product. Possible barbituric acid formation from 5-chlorouracil and 5-fluorouracil cannot be observed because of the relatively large rates of barbituric acid degradation under equivalent conditions. The greater portion of the hydrolysis in phosphate and borate buffer pH regions is a consequence of hydroxyl ion attack on the undissociated halouracil or the kinetically equivalent solvent attack on the monoanion and results in nonchromophoric products and no barbituric acid. Isobarbituric acid is obtained from 5-bromouracil degraded in oxygen-free bicarbonate buffer. It is not observable as a product in buffers under ambient conditions. Isobarbituric acid has a high degree of stability when air is excluded from the solution. The observed general base-catalyzed hydrolysis in buffer solutions can be explained by phosphate dianion attack on the undissociated halouracil and its monoanion and the kinetic dependencies have been determined. A small borate buffer catalysis exists in the cases of iodouracil and bromouracil. The rate of alkaline hydrolysis of bromouracil is the same as the rate of bromide ion production and proves that there is no appreciable storage in a reactive adduct that leads to products. 5-Methyluracil and uracil are highly stable under equivalent alkaline conditions and definitely implicate the need of a halogen substituent for facile hydrolysis of substituted uracils.

The alkaline solvolysis of 5-halouracils has not been delineated. Insight into the mechanism of action in biological systems and the need for synthetic routes for derived compounds such as glycosides demand fundamental physical organic and kinetic studies of the solvolytic transformations of these compounds.

Isobarbituric acid has been claimed as a product of the solvolysis of 5-bromouracil in the alkaline pH region.[2] It was isolated under specific conditions with $NaHCO_3$ as the reacting species. It was claimed that isobarbituric acid could not be obtained from the 5-halouracils in the presence of stronger bases because of the great instability of isobarbituric acid in alkali.[2]

We have systematically investigated the solvolysis of 5-fluoro, 5-chloro-, 5-bromo-, 5-iodo-, 5-methyl-, 5-hydroxy- (isobarbituric acid), and 6-hydroxyuracil (barbituric acid) in the entire pH region, in order to establish the log *k*–pH profiles for such solvolyses and to determine the routes and mechanisms of reaction as functions of the ionic state of the reacting species. We have obtained definite information that the major product of strong alkaline solvolysis of 5-halouracils is not isobarbituric acid but barbituric acid and that the routes of degradation are pH dependent.

Results

Spectral Changes and Product Identification.—The 5-halouracils are reasonably stable in acid.[3] Iodouracil is unstable in the presence of acid-degraded deoxyribose.[4,5] 5-Fluorouracil (FU) and 5-chlorouracil (CU) lose their ultraviolet absorbance at all wavelengths without any observed change in the chromophoric absorption band at all alkaline pH values greater than 5.6. Typical spectra as a function of time are given for CU in 0.22 *M* NaOH in Figure 1. Typical first-order plots for the loss of the spectral absorbance of CU and FU at various pH values are given for FU in Figure 2. The apparent first-order rate constants were calculated from the slopes of the plots of logarithms of absorbance *vs.* time and are listed in Table I.

The 5-bromouracil (BU) spectral changes for pH values below *ca.* 9.5 follow a similar pattern. The absorbance values at the λ_{max} disappear by apparent first-order processes without any observed changes in the chromophoric absorption band.

At pH values above 10, however, an initial increase in absorbance appears at 257 mμ and this new maximum can be distinguished from that assigned to the BU

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[1] Supported in part by Grants GM-09864-04,05 and CA-10738-06, National Cancer Institute, National Institutes of Health, U. S. Public Health Service, Bethesda, Md. H. J. Nestler is grateful to the Deutsche Forschungsgemeinschaft for his travel grant.

[2] S. Y. Wang, *J. Amer. Chem. Soc.*, **81**, 3786 (1959).

[3] E. R. Garrett, J. K. Seydel, and A. J. Sharpen, *J. Org. Chem.*, **31**, 2219 (1966).

[4] E. R. Garrett, T. Suzuki, and D. J. Weber, *J. Amer. Chem. Soc.*, **86**, 4460 (1964).

[5] E. R. Garrett, P. B. Chemburkar, and T. Suzuki, *Chem. Pharm. Bull.* (Tokyo), **13**, 1113 (1965).

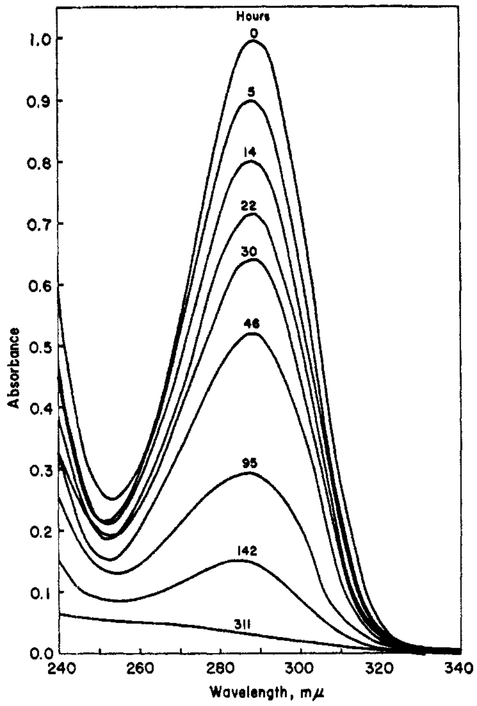

Figure 1.—Typical curves of the spectral changes of a 1.4 × 10^{-4} M chlorouracil in 0.218 M NaOH at 80.0°. Each curve is labeled as to the number of hours after the start of the degradation.

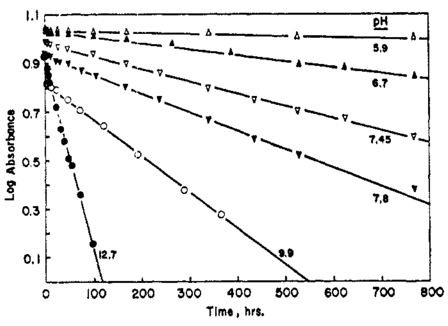

Figure 2.—Typical apparent first-order plots for the decrease in absorbance for fluorouracil at 80.0°. The curves of pH values 5.9, 6.7, 7.45, and 7.8 were in phosphate buffer and monitored at 265 mμ; pH 9.9 in borate buffer at 270 mμ; and pH 12.7 in 1.6 M NaOH at 295 mμ. The reactions were studied for more than 8 half-lives.

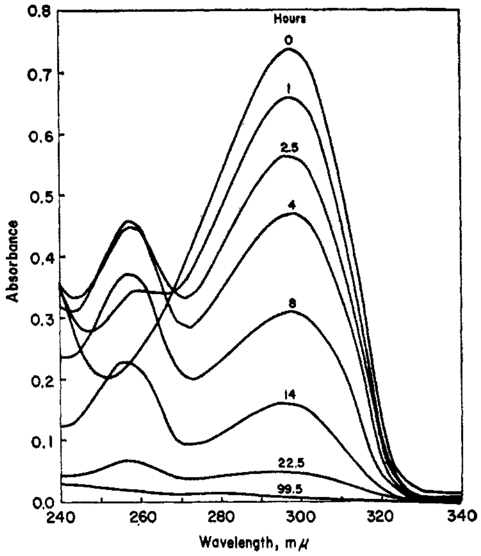

Figure 3.—Typical curves of the spectral changes of a 1.25 × 10^{-4} M bromouracil in 0.48 M NaOH at 80.0°. Each curve is labeled as to the number of hours after the start of the degradation.

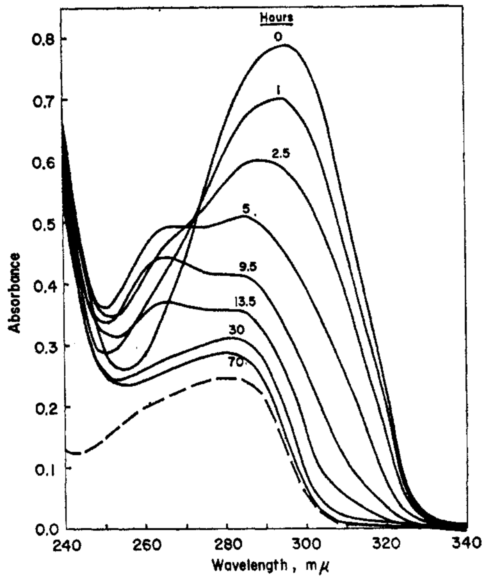

Figure 4.—Typical curves of the spectral changes of a 1.30 × 10^{-4} M iodouracil in 0.100 M NaOH at 80.0°. Each curve is labeled as to the number of hours after the start of the degradation. The dashed line is the spectrum of an 0.45 × 10^{-4} M solution of uracil in 0.100 M NaOH.

chromophore in the 285–300-mμ range (Figure 3). The absorbances at both maxima subsequently disappear with rates of the same order of magnitude. The absorbance at *ca.* 257 mμ was assigned to barbituric acid on the basis of the spectrophotometric pK'_a determination of the degrading BU and paper chromatographic separations. This is consistent with the reported isolation of 1-methylbarbituric acid with 1 N NaOH at 60° from 1-methyl-5-bromouracil.[6]

Iodouracil (IU) also forms barbituric acid as is indicated by the spectra of the alkaline degrading solution at various intervals (Figure 4) at pH values above 10.

The absorbances of the degrading solutions of IU at the various pH values do not decrease to zero as was the case with FU, CU, and BU. Residual absorbances remain at 259 or 283 mμ, dependent on the pH (Figure 4). These indications of uracil as a product were confirmed by paper chromatographic techniques. These residual absorbances at infinite time were used to calculate the yield of uracil from the observed absorptivities[3] of uracil at the pH of spectrophotometrically analyzed solutions. These pH values and the per cent yield of uracil from IU at the various pH values of degradation are also given in Table I.

The apparent first-order rate constants (Table I) for the degradation of BU and IU at various pH values were obtained from the slopes of first-order plots of absorbances at those wavelengths (290–310 mμ) where no spectral interference would be given by either barbituric acid (λ_{max} of anion = 257 mμ) or uracil (λ_{max} of anion = 283 mμ).

Log k-pH Profiles.—The log k-pH profiles were similar for all 5-halouracils (Figures 5 and 6) and were constructed from the apparent first-order rate constants, k, and pH values at 80° (Table I). As the alkali con-

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(6) J. J. Fox, presented in part at the XXIst Congress of the International Union of Chemistry, Prague, Sept 1967, personal communication.

TABLE I

APPARENT FIRST-ORDER RATE CONSTANTS (k IN SEC^{-1}) FOR THE HYDROLYSIS OF 5-HALOURACILS (10^{-4} M) AT 80.0°

	Buffers		10^6k[b]								
			FU[c]		CU[d]		BU[e]		IU[f]		% U
pH[a]	[$H_2PO_4^-$]	[HPO_4^{2-}]	Calcd	Exptl	Calcd	Exptl	Calcd	Exptl	Calcd	Exptl	from IU
5.90	0.068	0.010	0.025	0.029	0.54	0.30	0.93	0.84	2.03	1.74	59
6.70	0.025	0.025	0.13	0.16	0.76	0.93	1.70	1.94	3.87	3.87	46
7.45	0.006	0.031	0.39	0.35	1.23	1.26	2.77	2.77	4.00	4.40	30
7.80	0.002	0.033	0.50	0.51	1.30	1.20	3.23	2.96	4.03	3.94	20
	[H_3BO_4]	[NaOH]									
7.85	0.050	0.004	0.50	0.40	1.16	1.14	2.70	2.76	2.60	2.92	18
8.50	0.050	0.012	0.62	0.48	1.34	1.33	3.28	3.32	3.20	3.38	...
8.90[g]	0.050	0.021	0.67	0.68	1.39	1.40	3.34	3.40	4.10	3.75	16
9.50	0.050	0.037	0.74	0.82	1.44	1.40	4.04	3.50	3.95	3.74	8
9.90	0.050	0.044	0.86	0.96	1.51	1.48	4.57	3.68	4.60	4.13	16
10.50	...	0.0100	1.40	1.06	1.80	1.72	6.18	7.34	8.00	7.05	19
10.80	...	0.0194	...	...	...	...	8.55	6.55	12.5	12.6	11
11.10	...	0.040	2.72	2.14	2.80	2.93	12.4	14.6	19.0	18.4	...
11.50	...	0.100	3.87	3.89	3.41	3.63	19.2	22.2	33.0	43.8	40
12.08	...	0.400	5.19	5.70	4.32	4.61	29.0	28.0	51.0	51.2	...
12.20	...	0.535	5.44	5.81	4.51	4.15	29.8	31.5	56.7	59.0	60
12.50	...	1.00	5.69	5.43	4.67	5.06	31.7	32.1	62.0	57.4	71

[a] The pH values of phosphate and borate buffer solutions were read at 80.0° on the pH meter standardized at that temperature. The other pH values were calculated from pK_w − pOH where pOH = −log a[NaOH] where the activity coefficient a and the pK_w values were obtained from the literature.[12] The ionic strength was held constant at 0.1. [b] Additional values given in the order, XU, pH, NaOH, exptl 10^6k (calcd 10^6k) were CU, 11.2, 0.05, 2.93 (2.80); CU, 11.8, 0.218, 3.62 (3.98); FU, 12.25, 0.60, 5.62 (5.47); FU, 12.37, 0.80, 5.62 (5.57); IU, 11.75, 0.194, 48.8 (44.2) (with a yield of % U = 38%); BU, 11.45, 0.0962, 19.2 (18.2 with similar first-order rate constants for ionic strengths in the range 0.1–1.3). Registry no. are as follows: [c] 51-21-8; [d] 1820-81-1; [e] 51-20-7; [f] 696-07-1. [g] Initial concentrations of 5-halouracils of 0.5, 1.0, and 1.5 × 10^{-4} M and ionic strengths of 0.1, 0.2, and 0.3 gave very similar apparent first-order rate constants.

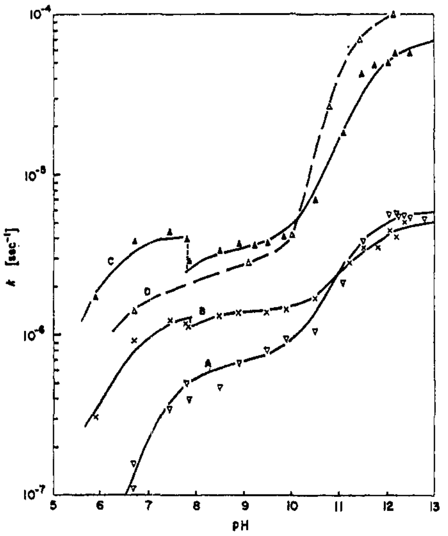

Figure 5.—The log k-pH profiles for fluorouracil, A; chlorouracil, B; iodouracil, C; and barbituric acid, D, at 80.0°. The solid lines are calculated. The discontinuities at pH 7.8 are due to the change in buffer type and are attributable to differences in magnitudes of buffer catalysis.

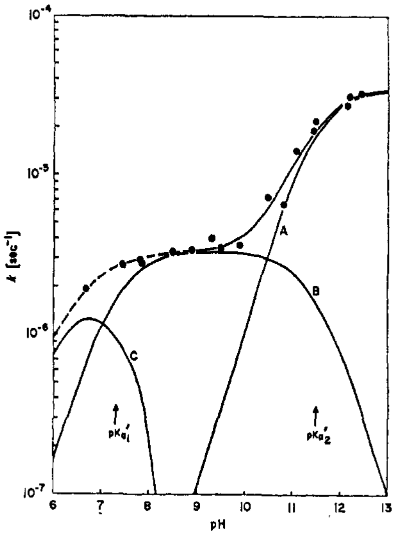

Figure 6.—Typical construction of the log k-pH profiles of 5-halouracils. The curve A is for bromouracil dianion attack by water. The curve B is for the bromouracil monoanion attack by water. The curve C is for the water and phosphate dianion attack on undissociated and monoanionic bromouracil at 80.0°.

centration increases and more of the 5-halouracils exist as dianions[7,8] (pH > pK'_{a_2} where pK'_{a_2} values are *ca.* 11.4 at 80°), the rate constants become relatively independent of pH. This is indicative of a water attack on the dianion. The kinetically equivalent hydroxyl ion attack on the monoanion may not be preferred as an explanation because of the absence of significant ionic strength effects in the strongly alkaline region which would be expected to affect ion–ion interaction.[9,10a] However, this may not be a conclusive argument because of the ionic-strength range employed.

As the pH decreases in the pH region of the pK_{a_2}' the rate constants also show definitive decreases concomitant with the transformation of the dianion into the monoanion. Apparent first-order rate constants for the solvolytic degradation of the 5-halouracil dianions in the high pH regions may be accounted for by eq 1 where k_0'' is the specific catalytic constant for the

$$k_{U^{2-}} = k_0''f_{U^{2-}} = k_0'' \frac{K'_{a_2}}{[H^+] + K'_{a_2}} \qquad (1)$$

attack of water on the dianion. The fraction of dianion present, $f_{U^{2-}}$ can be given in terms of the [H^+]

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(7) K. Berens and D. Shugar, *Acta Biochim. Polon.*, **10**, 25 (1963).

(8) I. Wempen and J. J. Fox, *J. Amer. Chem. Soc.*, **86**, 2474 (1964).

(9) E. R. Garrett, *J. Pharm. Sci.*, **51**, 811 (1962); *Advan. Pharm. Sci.*, **2**, 1 (1967).

(10) A. A. Frost and R. G. Pearson, "Kinetics and Mechanisms," 2nd ed, John Wiley and Sons, Inc., New York, N. Y., 1962: (a) p 150; (b) p 160.

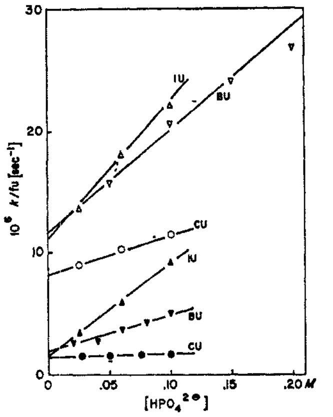

Figure 7.—The dependence of the quotient of the apparent first-order hydrolytic rate constant, k, and the fraction of undissociated halouracil, f_U, on the concentration of phosphate dianion at 80.0° at constant ionic strength 0.4. The open symbols are at pH 7.65 and the solid symbols at pH 6.70.

and the K'_{a_2}. This contribution to the over-all log k–pH profile is represented by curve A in Figure 6 for 5-bromouracil.

The contribution to the apparent first-order rate constant at *ca.* pH 9 was assigned to the attack of water on the 5-halouracil monoanion or its kinetic equivalent,[9] the attack of hydroxyl ion on the undissociated molecule. This is expected to be relatively invariant with pH in the pH region 8.5–10 which is ~1.5 pH units above the pK_{a_1}' and ~1.5 pH units below the pK'_{a_2}. This contribution to the over-all log k–pH profile (curve B, Figure 6) may be accounted for[11] by

$$k_{U^-} = k_0'f_{U^-} = \frac{k_0'}{[H^+]/K'_{a_1} + 1 + K'_{a_2}/[H^+]} = \frac{k_0'K'_{a_1}[H^+]}{[H^+]^2 + K'_{a_1}[H^+] + K'_{a_1}K'_{a}} \quad (2)$$

When $[H^+]/K'_{a_1} \ll 1$, eq 2 reduces to

$$k_{U^-} = k_0'f_{U^-} = \frac{k_0'}{1 + K'_{a_2}/[H^+]} = \frac{k_0'[H^+]}{[H^+] + K'_{a_2}} \quad (3)$$

for the special case when no undissociated halouracil is present, $f_U = 0$.

Similarly, when $K'_{a_2}/[H^+] \ll 1$, eq 2 reduces to

$$k_{U^-} = k_0'f_{U^-} = \frac{k_0'}{[H^+]/K'_{a_1} + 1} = \frac{k_0'K'_{a_1}}{[H^+] + K'_{a_1}} \quad (4)$$

for the special case when on dianion is present, $f_{U^{2-}} = 0$. The eq 4 is kinetically equivalent[9] to

$$k_{U^-} = k_{OH}[OH^-]f_U = \frac{k_{OH}[OH^-][H^+]}{[H^+] + K'_{a_1}} = \frac{k_{OH}K_w}{[H^+] + K'_{a_1}} \quad (5)$$

Since the pK'_{a_1} (*ca.* 7.3) and pK'_{a_2} (*ca.* 11.5) values are widely separated, eq 3 can be used for pH values >9 to construct the right-hand branch of curve B (Figure 6). Thus, for the proper choice of a pK'_{a_2} value, the sums of the antilogarithmic values of curves A and B are consistent with the observed rate constants plotted as their logarithms above pH 9.

The left-hand branch of curve B of Figure 6 was constructed (eq 4 or 5) from proper choices of k_0' and the K'_{a_1} values on the premise that no significant amount of dianion was present at pH values below 9.

The differences between the contributions of curve B and the experimentally obtained log k–pH profile below pH values of 9 permitted the construction of curve C, Figure 6. The only plausible explanations for this contribution were that the buffers acted as catalytic species and that the undissociated molecule is attacked by solvent. Kinetic studies of 5-halouracil solvolysis at constant pH values in the presence of various concentrations of phosphate and borate buffers confirmed these premises (Figures 7 and 8), since the apparent rate constants were linear and increasing functions of buffer concentrations.

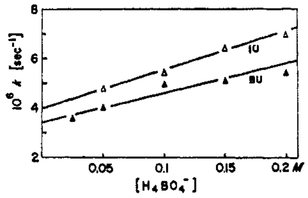

Figure 8.—The apparent first-order rate constant, k, for the hydrolysis of bromouracil and iodouracil plotted as a function of borate monoanion concentration, $[H_4BO_4^-]$ at 80.0° and at pH 9.3.

Buffer Catalysis.—The possible catalytic contributions to the apparent first-order rate constant for the solvolysis of 5-halouracils in the phosphate buffer region may be expressed by eq 6 where k_{HPO_4} and

$$k = (k_0 + k_{OH}[OH^-] + k_{HPO_4}[HPO_4^{2-}] + k_{H_2PO_4}[H_2PO_4^-])f_U + k'_{HPO_4}[HPO_4^{2-}]f_{U^-} \quad (6)$$

k'_{HPO_4} are the catalytic rate constants for the attack of phosphate dianion on undissociated and monoanionic 5-halouracil, respectively, and where $k_{H_2PO_4}$ and k_{OH} are the catalytic rate constants for the attack of phosphate monoanion and hydroxyl ion (eq 5) on the undissociated species, respectively. The fact of a water attack on the undissociated IU when a species is available to react with an equilibrated iodonium ion has already been demonstrated.[4,5]

Alternative contributions of $k'_{H_2PO_4}[H_2PO_4^-]f_{U^-}$ and $k_0'f_{U^-}$ are kinetically equivalent to $k_{HPO_4}[HPO_4^{2-}] \cdot f_U$ and $k_{OH}[OH^-]f_U$, respectively,[9,11] and thus are implicit in eq 6. The fractions of undissociated halouracil, f_U, and the monoanion, f_{U^-}, are implicit in the eq 4 and 5. Since $f_{U^-}/f_U = K'_{a_1}/[H^+]$ and $[H_2PO_4^-] = [HPO_4^{2-}][H^+]/K'_a$ where K'_a is the dissociation constant of monophosphate anion, the eq 6 can be rearranged to

$$k/f_U = k_0 + k_{OH}[OH^-] + (k_{HPO_4} + k'_{HPO_4}K'_{a_1}/[H^+] + k_{H_2PO_4}[H^+]/K'_a)[HPO_4^{2-}] \quad (7)$$

and the plots of k/f_U against the concentration of the phosphate dianion at constant pH and ionic strength should be linear of positive slope with intercept values of $k_0 + k_{OH}[OH^-]$. The specific rate constants obtained from these intercepts at the several pH values are consistent with the values listed in Table II. The specific values are given in the footnotes of this table. The validity of eq 7 is demonstrated by the curves of Figure 7. The fact that the slopes of such plots increase with increasing pH for IU, BU, and CU demand a significant catalytic contribution from the phosphate dianion attack on the 5-halouracil monoanion since $K'_{a_1}/[H^+]$ increases with increasing pH values. The fact that the converse is not true shows that the contribution of $k_{H_2PO_4}$ for the attack of phosphate mono-

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[11] E. R. Garrett, *Arzneim.-Forsch.*, **17**, 795 (1967).

TABLE II

CATALYTIC RATE CONSTANTS FOR THE SOLVOLYSIS OF 5-HALOURACILS AT 80.0°

	FU	CU	BU	IU
pK'_{a_1} [a]	7.3	7.2	7.3	7.4
pK'_{a_2} [a]	11.3	11.4	11.5	11.6
10^7k_0	0.0	5.0	6.0	10.0
$10^7k_0'$	6.6	14.0	33.0	34.0
$10^6k_0''$	6.0	5.0	35.0	70.0
k_{OH} [b]	0.141	0.385	0.705	0.575
$10^4k'_{OH}$ [b]	1.28	0.845	4.72	7.50
$10^5k_{HPO_4}$ [c]	0.0	0.0	2.41	10.0
$10^5k'_{HPO_4}$ [c]	...	0.78	1.47	1.51
$10^5k'_{H_4BO_4}$ [d]	...	...	1.20	1.55

[a] These pK_a' values were obtained from the best fit of the log k–pH profile where the ionic strength is 0.1 according to the expression for the apparent first-order rate constant at constant pH

$$k = (k_H[H^+] + k_0 + k_{HPO_4}[HPO_4^{2-}])f_U + (k_0' + k'_{HPO_4}[HPO_4^{2-}] + k'_{H_4BO_4}[H_4BO_4^-])f_{U^-} + k_0''f_{U^{2-}}$$

where f_U, f_{U^-}, and $f_{U^{2-}}$ are the fractions of the total halouracil concentrations that are undissociated, nonoanionic, and dianionic respectively; the k_H values, which are only significant for IU in the presence of a reducing species have been published previously.[4] The pK'_{a_1} values are reasonably consistent with the estimates obtained at the pH of half-neutralization at 80°, but at an ionic strength of 0.1 and are IU, 7.40; BU, 7.42; CU, 7.42; and FU, 7.5. [b] The k'_{OH} and k_{OH} values are obtained from $k'_{OH}[OH^-]f_{U^-}$ and $k_{OH}[OH^-]f_U$ which are kinetically equivalent to $k_0''f_{U^{2-}}$ and $k_0'f_{U^-}$ since $k_{OH}[OH^-] = k_0f_{U^-}/f_U$ and $k'_{OH} = k_0f_{U^{2-}}/f_{U^-}[OH^-]$ where $[OH^-] = 10^{-(pK_w-pH)}$; pK_w values at 80° were determined from the literature.[12] [c] The values obtained from the slopes of the apparent first-order rate constants divided by the fraction undissociated, k/f_U, against $[HPO_4^{2-}]$ at pH values of 6.70 and 7.65 at 80° where the slopes were defined as $[k_{HPO_4} + k'_{HPO_4}K'_{a_1}/[H^+]]$ where the pK'_{a_1} were taken as CU, 7.0, BU, 7.1, and IU, 7.2 at the ionic strength of 0.4 used in these studies were consistent with the values given in the table from best fit of the log k–pH profile. They were $10^5k'_{HPO_4} = 1.51$, $10^5k_{HPO_4} = 7.1$ for IU. The intercept of these plots give values of $k_0 + k_0'f_{U^-}/f_{U^{2-}}$. From the two intercepts at pH 6.70 and 7.65, *i.e.*, 1.5×10^{-6} and 11.1×10^{-6}, the derived values of $k_0 = 7.6 \times 10^{-7}$ and $k_0' = 37.0 \times 10^{-7}$ were in good agreement with the value obtained by best fit of the log k–pH profile for IU. The values for the k_{HPO_4} and k'_{HPO_4} constants obtained from plots of k/f_U against HPO_4^{2-} were the same as given for the best log k–pH fit for BU and CU. The respective intercepts of such plots for BU at pH values of 6.70 and 7.65 were 2×10^{-6} and 11.6×10^{-6} and the derived values of $k_0 = 8 \times 10^{-7}$ and $k_0' = 31 \times 10^{-7}$ were in good agreement with the values obtained by best fit of the log k–pH profile for BU. The respective intercepts of such plots for CU at pH values of 6.70 and 7.65 were 1.41×10^{-6} and 8.2×10^{-6} and the derived values of $k_0 = 7 \times 10^{-6}$ and $k_0' = 1.41 \times 10^{-7}$ were in good agreement with the value obtained by best fit of the log k–pH profile for CU. [d] These values were obtained from the apparent slopes of the apparent first-order rate constants against $[H_4BO_4^-]$ at pH values of 9.3 at 80° where the slopes were defined as $k'_{H_4BO_4}f_{U^-}$.

anion on undissociated 5-halouracil is of lesser significance.

The assumption that $k_{H_2PO_4}$ is negligible is consistent with the agreement of calculated values of k (eq 6) with the experimental values (Table I) on the premise that $k_{H_2PO_4} = 0$. The estimates of k_{HPO_4} and k'_{HPO_4} listed in Table II were obtained from the slopes of the plots at the several pH values of Figure 7 in accordance with the eq 7 for $k_{H_2PO_4} = 0$ and from the best estimates of fit of the log k–pH curves of Figures 5 and 6. The values from both sources showed good agreement (Table II). A small borate buffer catalysis exists in the IU and BU cases. The specific catalytic rate constants on the assumption that monoborate ion is the major contributing species are derived from the slopes of Figure 8 and are given in Table II. The solid lines in Figures 5 and 6 represent the calculated log k–pH rate profiles with buffer effects considered whereas the points are experimental values. The discontinuities at *ca.* pH 8 are due to the change from phosphate to borate buffers where the buffer catalytic effects are much less. The dashed line in Figure 5 is the log k–pH profile for barbituric acid degradation determined under corresponding conditions. The pH values in NaOH solutions were calculated from $-\log [H^+]$ where $[H^+] = K_w/a_{NaOH}[NaOH]$ where the activity coefficients a_{NaOH} and K_w values were obtained from the literature.[12]

Estimation of Rate Constants for Parallel Reactions.—Barbituric acid (BA) shows a distinct band at 257 mμ which appears concomitantly with the disappearance of the IU and BU maxima in alkaline solutions and then subsequently disappears with time (Figures 3 and 4). A general model for the kinetics of solvolysis of the halouracils (XU) would be

$$\begin{tikzcd} \text{XU} \arrow[rr, "k_{BA}"] \arrow[d] \arrow[dr, "k_{NC}"] & & \text{BA} \arrow[dl, "k_2"] \\ \text{U} & \text{nonchromophoric or rapidly degrading products (NC)} & \end{tikzcd} \tag{8}$$

The apparent first-order rate constants, k_2, were obtained from the loss of the absorbance at 257 mμ of BA under equivalent conditions. The $k_1 = k_U + k_{BA} + k_{NC}$ values for the loss of XU were obtained from the apparent first-order loss of absorbance at 290 mμ for BU and at 310 mμ for IU where the molar absorptivity of barbituric acid, $\epsilon^{BA} \sim 0$, would not interfere and the absorbance of U would not interfere in the case of IU.

The amounts of uracil, $[U]_\infty$ as a final product were obtained from the absorbances at the completion of the reactions when all BA had degraded and made no contribution to the spectra. Since U is a product of IU in parallel reactions[10b] (eq 8), it follows that

$$k_U = k_1[U]_\infty/[XU]_0 \tag{9}$$

where $[XU]_0$ is the initial concentration of the halouracil. The other halouracils did not give uracil as a product; *i.e.*, $k_U = 0$ for BU, CU, and FU.

The absorbance at 260 mμ, A_{260}, is a linear function of the absorbances of XU, BA, and U

$$A_{260} = \epsilon_{260}^{BA}[BA] + \epsilon_{260}^{XU}[XU] + \epsilon_{260}^{U}[U] \tag{10}$$

where the ϵ values are the respective absorptivities. This absorbance is hypersensitive to barbituric acid since $\epsilon_{260}^{BA} = 20{,}000$, whereas IU, BU, and U have absorptivities below 5000 above a pH of 10.

If the hydrolysis products of the halouracils are only barbituric acid and uracil the concentration of barbituric acid at any time can be predicted[13] from the obtained values of the rate constants k, for the over-all loss of XU, k_2 for the degradation of BA, and k_U (eq 9) by eq 11 where $k'_{BA} = k_1 - k_U$.

$$BA_{predicted} = [XU]_0 \frac{k'_{BA}}{k_2 - k_1}(e^{-k_1t} - e^{-k_2t}) \tag{11}$$

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[12] H. S. Harned and B. B. Owen, "The Physical Chemistry of Electrolytic Solutions," 3rd ed, Reinhold Publishing Corp., New York, N. Y., 1958.

[13] E. R. Garrett, *J. Amer. Chem. Soc.*, **80**, 4049 (1958).

TABLE III

RATE CONSTANTS AND YIELDS IN THE HYDROLYSIS OF 5-IODO- AND 5-BROMOURACIL TO URACIL, BARBITURIC ACID, AND NONCHROMOPHORIC PRODUCTS AT 80.0°

pH[a]	10^6k_1[b]	10^6k_2[c]	% U	% BA	% NC	10^6k_U[d]	10^6k_{BA}[e]	10^6k_{NC}[f]
				IU				
7.8	4.0	2.4	20	0.5	79.5	0.8	0.02	3.2
9.0	4.8	2.4	16.5	6.0	77	0.8	0.3	3.7
10.9	12.6	27	10	45	45	1.3	5.7	5.7
11.1	18.4	48	46	45	9	8.5	8.3	1.6[h]
11.5	43.8	72	40	36	24	17.5	15.8	10.5
11.8	50.0	80	38	41	21	19.0	20.4	10.6
12.2	59.0	105	60	40	0	36	23	...
12.5	57.4	120	70	30	0	40	17	...
				BU[g]				
10.5	7.34	13.5	...	*Ca.* 30	*Ca.* 70	...	2.2	5.1
10.8	6.6	27.5	...	65	35	...	4.3	2.3[h]
11.5	20.6	71.2	...	58	42	...	12.0	8.6
12.2	31.5	100	...	74	26	...	23.3	8.2

[a] Observed pH values in phosphate (7.8), borate (9.0), and Na_2CO_3 (10.5) buffers. Calculated pH values[12] from $pH = pK_w - pOH$ where $pOH = -\log a_{NaOH}[NaOH]$ in the other instances where NaOH solutions were used. [b] Over-all first-order rate constant for the hydrolysis of IU and BU. [c] First-order rate constants for the degradation of barbituric acid to nonchromophoric products and interpolated in some instances from the obtained data: 10^6k_2, pH; 1.43, 6.7 (phosphate); 2.92, 9.0 (borate); 4.26, 10.0 (borate); 15.8, 10.45 (0.01 *N* NaOH); 26.7, 10.8 (0.0194 *N* NaOH); 71.2, 11.45 (0.097 *N* NaOH); 103, 12.15 (0.485 *N* NaOH). In 0.254 *N* HCl, $k = 5.81 \times 10^{-7}$ sec^{-1}. [d] First-order rate constant for uracil formation estimated from the fraction of IU that forms uracil times the over-all first-order rate constant (k_1). [e] First-order rate constant for barbituric acid formation estimated from observed absorbance values at 260 mμ as a function of time from known absorptivities of U, XU, and BA and from the k_2 values for the degradation of barbituric acid. [f] $k_{NC} = k_1 - k_{BA} - k_U$. [g] In borate buffer at pH 9.3 no significant amount of barbituric acid as a hydrolytic product was observed. [h] These values appear to be out of sequence and were ignored in the fitting of log *k*–pH profiles for the microscopic rate constants.

The actual amount of barbituric acid, BA_{actual}, was calculated at any time, *t*, on rearrangement of eq 10 from the absorbance at 260 mμ, the known absorptivities of BA, XU, and U, and the relations given in eq 12

$$XU = [XU]_0e^{-k_1t} \tag{12}$$

$$U = [XU]_0\,(1 - e^{-k_1t})\,k_U/k_1 \tag{13}$$

and 13 where k_u is obtainable from eq 9 and eq 14 describes the true dependency of BA_{actual} on time.

$$BA_{actual} = [XU]_0\,\frac{k_{BA}}{k_2 - k_1}\,(e^{-k_1t} - e^{-k_2t}) \tag{14}$$

The ratio of the values $BA_{actual}/BA_{predicted}$ at any time from eq 11 and 14 is

$$BA_{actual}/BA_{predicted} = k_{BA}/k'_{BA} = k_{BA}/(k_1 - k_U) \tag{15}$$

from which k_{BA} can be calculated and also the apparent rate constant to nonchromophoric products, $k_{NC} = k_1 - k_U - k_{BA}$. The values of these ratios were obtained over wide intervals of A_{260} *vs.* time plots.

The resultant rate constants are listed in Table III for BU and IU at various pH values. A typical analog computer fitting of the measured absorbances as a function of time that substantiates the validity of the derived rate constants for eq 8 (Table III) is given in Figure 9.

The apparent first-order rate constants for BA degradation were more than ten times greater than the apparent first-order rate constants for CU and FU degradation above pH 10.5 (Figure 5). Thus, if BA were a hydrolytic product, it could not be experimentally observed even if $k_{BA} = k_1$.

The data for the log *k*–pH profiles for the hydrolysis of 5-bromo- and 5-iodouracil in the alkaline pH regions to the several products, *i.e.*, k_{BA}, k_U, and k_{NC}, are plotted in Figure 10 and are based on the values of Tables I and III.

When the apparent first-order rate constant for the solvolysis of IU is corrected for the route to uracil, it is astonishing how close the apparent rate constants are for the formation of barbituric acid and nonchromophoric products from both IU and BU (See Figure 10). In fact the same kinetic dependencies can satisfy both compounds. They are

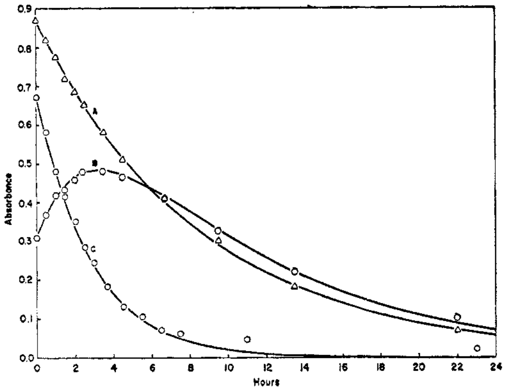


Figure 9.—Typical fitting of analog computer program to the measured absorbances at 290 mμ, curve A, and at 260 mμ, curve B, as a function of time for the degradation of bromouracil in 0.535 *N* NaOH (pH 12.2) at 80.0°. The loss of absorbance at 260 mμ of barbituric acid with time under similar conditions is also shown, curve C.

$$k_{BA} = (k'_{OH})_{BA}[OH^-]f_{U^-} = (k_0'')_{BA}f_{U^{2-}} \tag{16}$$

for the attack of the hydroxyl ion on the fraction of halouracil as the monoanion f_{U^-} or the kinetically equivalent attack of solvent on the fraction as the dianion, $f_{U^{2-}}$

$$k_{NC} = (k_0')_{NC}f_{U^-} + (k_0'')_{NC}f_{U^{2-}} \tag{17}$$

which could be alternatively interpreted as the sum of the hydroxyl ion attacks on the undissociated fraction, f_U, and fraction as the monoanion, f_{U^-}

$$k_U = (k_0)_Uf_U + (k_0'')_Uf_{U^{2-}} \tag{18}$$

This last equation holds only for IU since $k_U = 0$ for BU. The latter term is kinetically equivalent to

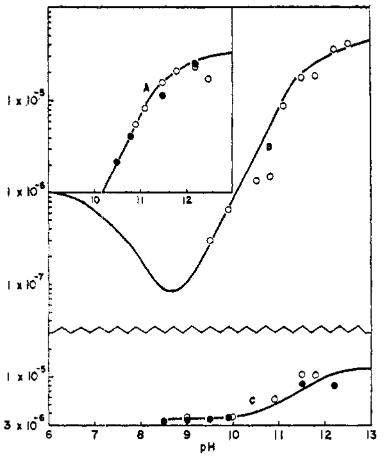


Figure 10.—The log k–pH profiles for the rate constants for product formation from 5-bromouracil (solid circles) and 5-iodouracil (open circles) at 80.0°. The labeled curves are A, k_{BA} for barbituric acid formation; B, k_U for uracil formation; C, k_{NC} for production of nonchromophoric products.

hydroxyl ion attack on the fraction of IU that is the monoanion, f_{U^-}.

The microscopic rate constants at 80.0° that reasonably describe the apparent first-order rate constants of Figure 10 and Table III are $(k'_{OH})_{BA} = 2.95 \times 10^{-4}$ l./mol sec^{-1}, $(k_0'')_{BA} = 3.35 \times 10^{-5}$ sec^{-1}, $(k_0')_{NC} = 3.5 \times 10^{-6}$ sec^{-1}, $(k_0'')_{NC} = 1.2 \times 10^{-5}$ sec^{-1}, $(k_0'')_U = 4.0 \times 10^{-5}$ sec^{-1}. Also, $(k_0)_U = 10^{-6}$ sec^{-1} from the literature[4] on the reasonable assumption that an oxidizable species is among the nonchromophoric products of IU that can reduce the positive iodonium ion that dissociates in a reversible equilibrium from the nonionized IU. The lines drawn in Figure 10 are calculated from eq 16–18 on the basis of these rate constants where f_U, f_{U^-}, and $f_{U^{2-}}$ are implicitly defined in eq 1–5. The K'_{a_2} value used was 2.6×10^{-12}; $pK'_{a_2} = 11.6$ where $pK_w = 12.63$ at 80.0°.

Estimates of the Arrhenius parameters for the hydrolysis of the 5-halouracils at various pH values were obtained from the slopes and intercepts of plots of the logarithm of the apparent first-order rate constants, k, against the reciprocals of the absolute temperatures, T, in accordance with eq 19 where R is in 1.987 cal deg^{-1}

$$\log k = \log P - E_a/2.303RT \qquad (19)$$

mol^{-1} and the various k, log P, and ΔH_a values for the several pH values are listed in Table IV.

The Stability of Thymine and Isobarbituric Acid.—Thymine, 5-methyluracil, is highly stable in alkali. The ultraviolet spectrum when monitored at 80° in 0.01 N NaOH with intermittent oxygen purging remained unchanged over 8 days.

However, isobarbituric acid, 5-hydroxyuracil, loses its chromophore almost instantly at 80° in 0.5 N NaOH. Detailed studies of its decomposition at less strenuous conditions gave extremely erratic results. The ultraviolet chromophore, λ_{max} 315 mμ, disappeared with time without any apparent shift in the λ_{max} or changes in the ratios of the absorbances at several wavelengths. Degradations in alkaline solutions between 0.01 and 0.1 N NaOH were primarily zero order for more than 70% of the total reaction under ambient conditions and showed very little variation with alkaline concentrations. At 2×10^{-4} M isobarbituric acid, the rates of per cent absorbance decreasing with time were (in °C, %/min) 30°, 6; 34°, 5; and 40°, 2. This decrease in the apparent zero-order rate with temperature is consistent with the decreased solubility of oxygen when oxidative degradation is postulated.[2] In the alkaline range, 0.1–0.4 N NaOH, the degradation of the chromophore is apparently first order for the greater period of degradation but there does not appear to be a systematic dependence on NaOH concentration. Orders of magnitude are 1 to 4×10^{-4} sec^{-1} between 25 and 40°. When isobarbituric acid was maintained under an oxygen-free nitrogen atmosphere in borate buffer at 60°, there was less than 10% loss of absorbance in 700 hr at pH 8. When this was not done at 40°, there is a 14% loss in 175 min at pH 8.0 whereas if the water was prepurged with nitrogen this amount of decomposition takes 525 min.

Table IV

Apparent First-Order Rate Constants (10^6k in sec^{-1}) for the Hydrolysis of 5-Halouracils at Various Temperatures

	pH of borate buffers			NaOH, N	
	7.90	8.90	9.90	0.01	0.40[a]
			FU		
80.0°	0.396	0.63	0.96	1.06	5.75
70.0°	0.150	. . .	0.32	0.42	2.71[b]
60.0°	0.029	0.078	0.118	0.128	0.95
E_a	30.9	24.4	24.4	23.7	23.3
Log P	12.7	8.90	9.08	8.65	8.20
			CU		
80.0°	1.14	1.42	1.48	1.72	4.61, 4.71, 5.64
70.0°	0.405	0.514	0.563	0.695	2.67
60.0°	0.152	0.200	0.222	0.275	0.88, 0.83
E_a	23.7	22.2	21.9	21.1	21.6
Log P	8.70	7.85	7.70	7.30	8.10
			BU		
80.0°	2.76	3.50	3.68	5.08	36.3
70.0°	. . .	. . .	. . .	2.1	14.1, 12.8
60.0°	0.435	0.556	0.583	0.715	5.73
E_a	21.6	21.8	21.4	21.8	21.5
Log P	7.82	8.02	7.87	8.30	8.82
			IU		
80.0°	2.92	3.75	4.13	7.05	. . .
70.0°	1.15	1.41	1.66	3.00	. . .
60.0°	0.425	0.583	0.595	0.850	. . .
E_a	21.8	21.8	23.2	24.4	. . .
Log P	8.25	8.12	8.90	9.34	. . .

[a] Additional values obtained in 0.40 N NaOH were at 75.0° and were XU, 10^6k; FU, 4.86; CU, 3.90; and BU, 21.5. [b] Actually at 72.0°.

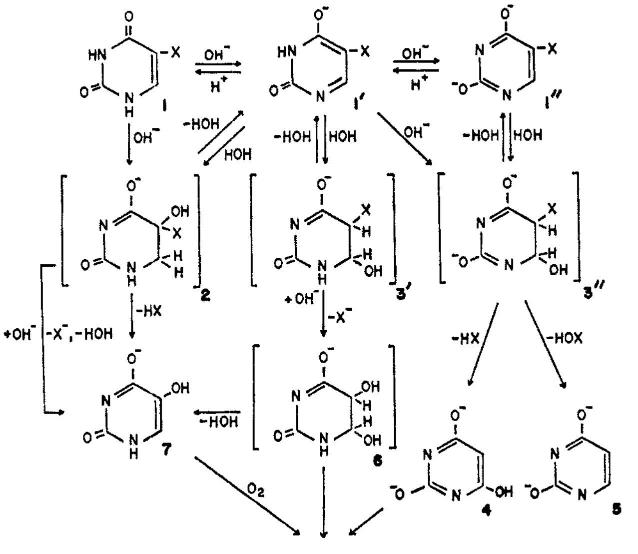
The degradation of BU under a nitrogen atmosphere at reflux temperatures for 22 hr produced crystals that when filtered off demonstrated the same spectral qualities in acidic and basic solution as isobarbituric acid, confirming the observation of Wang.[2]

In 1.5×10^{-2} M $NaHCO_3$ and pH 8.2 at 80°, the $k = 5.63 \times 10^{-6}$ sec^{-1} for BU degradation whereas, in other buffers at similar pH values, the apparent first-order rate constants are less: *viz.*, $k = 2.96 \times 10^{-6}$, phosphate, pH 8.2; $k = 2.7 \times 10^{-6}$, borate, pH 7.9; $k = 3.3 \times 10^{-6}$, borate, pH 8.5.

Discussion

The alkaline hydrolysis of 5-halouracils is generally in the decreasing order IU > BU > CU > FU (Tables I–IV and Figures 5 and 6) in contrast to the high alkaline stability of uracil which degrades slowly by a first-order process with an apparent first-order rate constant of 4 × 10^{-7} sec^{-1} at 80° in 0.2 *N* KOH by measurement of the disappearance of the 281-mμ chromophore. 5-Methyluracil, thymine, and 5-carboxyuracil[14] are highly stable under equivalent conditions; the latter slowly degrades by decarboxylation to uracil.[14] Thus, the 5 halogen is implicated in the solvolysis. The observed production of barbituric acid (**4**) from IU and BU, consistent with the known kinetic dependencies (eq 16), can be formulated as a dehydrohalogenation of the reactive intermediate **3′′** on tautomeric rearrangement after direct hydroxyl ion attack on the 6 position of the monoanion **1′**. Alternatively barbituric acid production may result from dehydrohalogenation after the kinetically equivalent hydration of the 5,6 double bond of the dianion **1′′** to give the reactive intermediate **3′′**. The structures in Scheme I are given in accordance with the literature assignments.[7,8] In order to conserve space only one of the equivalent tautomeric forms is given.

SCHEME I
HYDROLYTIC ROUTES OF 5-HALOURACIL



The specific case of IU where uracil (**5**) is a significant product may be readily explained by the elimination of hypoiodous acid from the reactive dianion intermediate, **3′′**, which is consistent with the known kinetic dependency (eq 18) and previous demonstrations that the deiodination of IU occurs through the loss of a positive iodonium ion.[4,5] Alternatively, hydroxyl ion attack on the monoanion **1′** to form the reactive intermediate **3′′** is kinetically equivalent. The HOI can be readily disproportionated into periodate and iodide ions[5] under the alkaline conditions employed and is most probably readily reduced by products such as the barbituric acid derivatives.[4] In acid solution where an oxidizable species is not produced, present, or added, the iodonium ions and uracil (**5**) equilibrate with IU, where the equilibrium favors IU.[4,5]

The fact that the degradation of the anions of BU or IU (**1′** or **1′′**) cannot be completely accounted for by barbituric acid (**4**) or uracil (**5**) production implies that the chromophoric ring structure also undergoes rapid destruction. Possible routes to nonchromophoric products that may explain these phenomena are consistent with the observed kinetic dependencies (eq 17) and can produce unstable dihydropyrimidine derivatives, **1′** → **3′** → **6**, and isobarbituric acid by **1** → **2** → **7** or by **1′** → **2** → **7** or from **6** → **7**. Both of these potential products, **6** or **7**, would degrade rapidly under the conditions of these studies and would not contribute to the spectral absorbances monitored in the kinetic studies.

Barbituric acid must not be formed in the phosphate or borate pH buffer regions since it is degraded more slowly (Figure 5) and has higher absorptivity than the parent 5-halouracils and yet was not spectrally observed. This product must arise from the monoanion **1′** or the dianion **1′′**. The isolation of isobarbituric acid in oxygen-free bicarbonate buffer confirms its formation as the major product in the buffer region, pH 7–10. Isobarbituric acid is highly susceptible to oxidative degradation by atmospheric oxygen in the mildly alkaline region but is thermally stable under anerobic conditions even at elevated temperatures. The fact that degradation rates of BU in $NaHCO_3$ are higher than could be accounted for by the pH effects implies a catalytic effect by bicarbonate.

General base effects with borate and phosphate buffers demonstrate that the anions of these buffers are implicated in the degradation sequences and can readily be explained by their effectiveness in promoting the **1** → **2**, **2** → **7**, and **3′** → **6** sequences by general base catalysis where the first route is more consistent with the observed lack of ionic strength effects on the apparent first-order rate constants.

The rate of production of bromide ion from BU in alkali parallels the rate of loss of the BU chromophore. This fact indicates that proposed intermediates such as **3′** and **3′′** are truly highly reactive.

The possible formation of barbituric acid at pH values >10 as an intermediate in the FU and CU cases could not be readily monitored since the rate of degradation of BA is more than ten times that of these 5-halouracils (Figure 5). However, the dependence of their apparent rate constants on pH is of the same general character as IU and BU although the over-all rate constants are much less. The coincidence of the rate constants for barbituric acid and nonchromophoric product formation, k_{BA} and k_{NC}, from both IU and BU is of interest (Figure 10) and favors those reactions where the relative electronegative character of the iodo or bromo groups would have the least effects.

The fact that 5-methyluracil is highly stable in alkali does not deny the possibility of a reversible hydration of the 5,6 double bond but does further demonstrate that the elimination or substitution of a halogen is a prerequisite for further reaction.

Experimental Section

Materials.—The compounds studied were 5-chlorouracil (CU) and 5-methyluracil (MU) obtained from Calbiochem, Los Angeles, Calif., 5-fluorouracil (FU), 5-iodouracil (IU), and isobarbituric acid (OHU) obtained from K & K Laboratories, Inc., Plainview, N. Y., and barbituric acid (BA) and uracil (U) obtained from Eastman Organic Chemicals, Rochester, N. Y. Further samples of 5-fluorouracil were kindly donated by Drs. J.

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[14] H. J. Nestler and E. R. Garrett, *J. Pharm. Sci.*, submitted for publication.

R. Hoover and R. H. Blythe of Smith Kline and French Laboratories, Philadelphia, Pa., and by Hoffmann-La Roche, Nutley, N. J. These compounds, their structures, and principal ultraviolet spectral data have been given previously.[3–5] Solutions of these compounds were prepared with nitrogen-purged distilled water.

Kinetic Measurements.—The isothermal reactions were started by addition of a known small volume of the concentrated aqueous solution of the respective uracil compound to thermally equilibrated alkaline or buffer solutions in Pyrex volumetric flasks. The resultant concentration, generally 1.5×10^{-4} *M*, was suitable for direct spectrophotometric readings of aliquots with time on the Cary recording spectrophotometer Model 15 or Beckman DU spectrophotometer.

Reactions such as with HOU with oxygen excluded were carried out in 100-ml serum vials, sealed with rubber caps. Two valved injection needles were inserted into the rubber cap. The samples were taken through the one needle below the surface by a syringe while nitrogen was passed through the other needle above the surface. A positive nitrogen pressure was maintained inside the vial at all times.

Fast reactions such as with HOU at temperatures up to 50° were carried out in the thermostatically controlled cells of the spectrophotometer and the absorbances were monitored at intervals on a recorder.

Apparent first-order rate constants at the various specified buffer compositions (Tables I and IV) for the loss of the halouracil were obtained from the slopes of the logarithm of the absorbances plotted against time. Some typical first-order plots are given in Figure 2. In those cases where no spectrophotometrically absorbing species arose during the solvolysis, *viz.* FU, CU under all pH conditions and for BU and IU below pH 10 (see Figure 1), the absorbance at the pH-dependent λ_{max} at the specified pH was used. In the case of IU where a stable and absorbing uracil product was obtained, (see Figure 4) the logarithms of the differences between the absorbances and the final absorbance plotted against time permitted the calculation of the first-order rate constants which gave the same estimated first-order rate constants for all wavelengths. The apparent first-order rate constants at pH values greater than 10 were obtained from the absorbances at 290 mμ for BU (Figure 3) and 305 or 310 mμ for IU (Figure 4). At these wavelengths, there is no interference from the spectrum of BA and in the latter case, there is no interference from the spectrum of U.

No differences in the apparent first-order rate constants, *k*, for the hydrolysis of various uracils were observed in the presence and absence of oxygen. For example, under ambient conditions at 80.0°, in 0.485 *M* NaOH $k_{BU} = 27.6 \times 10^{-6}$ sec^{-1} whereas, under oxygen-free conditions, $k_{BU} = 28.0 \times 10^{-6}$ sec^{-1}. At 80° in 0.218 *M* NaOH, under ambient conditions, $k_{IU} = 49.7 \times 10^{-6}$ sec^{-1} whereas, under oxygen-free conditions in 0.194 *M* NaOH, $k_{IU} = 48.8 \times 10^{-6}$ sec^{-1}. No difference was observed for BA in 0.01 *M* NaOH at 80.0° for ambient and oxygen-free conditions, $k_{BA} = 1.58 \times 10^{-5}$ sec^{-1}.

When oxygen was bubbled through solutions of the 5-halouracils degrading in NaOH solutions, the apparent first-order rate constants were no different from those from similar studies conducted on these compounds prepared in nitrogen-purged water.

On variation of 5-halouracil concentration in borate buffer, pH 8.90, at 80.0° among 0.5, 1.0, and 1.5×10^{-4} *M* levels, no significant differences in apparent first-order rate constants were observed. The respective data were in the order (XU, 10^6k) FU, 0.685, 0.625, 0.630; CU, 1.43, 1.45, 1.39; BU, 3.18, 3.53, 3.52; IU, 3.70, 3.71, 3.56.

Ionic strength effects were studied for CU, BU, and IU in borate buffer solution, pH 8.90, at 80.0°. There were no significant differences among the apparent first-order rate constants (Table I) for $\mu = 0.1, 0.2$, and 0.3. The apparent first-order rate constants for BU in 0.0962 *M* NaOH, pH 11.45, at 80.0° were obtained at various ionic strengths and did not significantly vary ($10^6k_{BU}, \mu$): 19.2 and 20.6, 0.1; 21.3, 0.3; 22.0, 0.5; 21.4, 0.9; 23.8, 1.3.

An Orion bromide ion activity electrode, model 94-35, was used with a calomel reference electrode to follow bromide ion production from 10^{-2} *M* BU solvolysis in 0.481 *M* NaOH at 80.0°. Aliquots (4.00 ml) of the degrading solution were taken as a function of time and diluted with 4.00 ml of *ca.* 0.5 *M* $HClO_4$ to give pH *ca.* 1.0. The resultant emf was used to determine the bromide ion concentration from a calibration curve made up from the potentials of known amounts of NaBr prepared in a similar manner so that the high ionic strength and the pH of the reference and monitored solutions were the same. The apparent first-order rate constant for bromide ion formation was obtained from the linear slope of the logarithm of the difference of the final bromide ion concentration and that at any time plotted against time and was 3.3×10^{-5} sec^{-1}. Simultaneously, similar aliquots were diluted 1:100 and monitored spectrophotometrically (at 297 mμ) and the apparent first-order rate constant was 2.92×10^{-5} sec^{-1}.

The pH values of the buffer solutions were read at the temperature of the kinetic study with Beckman 41260 or 40495 glass electrodes, appropriate for high alkalinities and temperatures, in conjunction with a calomel reference electrode and a Radiometer pH meter (Copenhagen) which had been standardized with pH 7 and pH 10 buffers (Sargent Co.) at the same temperatures. The pH values of the sodium hydroxide solution were calculated from $pK_w - pOH$ where $pOH = -\log a_{NaOH}[NaOH]$ where the activity coefficient a_{NaOH} and the pK_w values were obtained from the literature[12] for the appropriate temperature.

The simulation of the kinetics of spectral absorbance changes was performed by means of a Pace analog computer, TR-10 (Electronic Associates, Long Branch, N. J.)

Chromatographic Identification of Reaction Products.—Aliquots (25 μl) of solution (10^{-2} *M*) were spotted on 20 × 10 cm Whatman no. 1 paper strips. The chromatograms were developed in closed tanks with a mixture of *t*-butyl alcohol, methyl ethyl ketone, ammonium hydroxide solution, and water (40:30:20:10).[15] The solvent front advanced 12–13 cm in approximately 3 hr. The spots were visualized under ultraviolet light (254 mμ) or with iodine vapor. Barbituric acid could also be detected by a yellow color formed on the paper.[16]

BU, 2×10^{-2} *M*, was heated at 80° in 0.5 *M* NaOH for the 4.5 hr at which it could be predicted that barbituric acid would be in maximum yield on the basis of the known rate constants (Tables I–III) and on the assumption of the sequence BU → BA → products. This degraded solution was paper chromatographed and demonstrated BU (R_f 0.59), BA (R_f 0.30), and NaOH (R_f 0.1) in agreement with the behavior of the paper chromatographed control solutions. The latter was observed with I_2 vapor.

IU, 2×10^{-2} *M*, was heated at 80° in 0.5 *M* NaOH for 4.5 hr. This degraded solution was paper chromatographed and demonstrated IU (R_f 0.68), U (R_f 0.52), BA (R_f 0.30) on uv identification and NaOH (R_f 0.1) and iodide ion (R_f 0.75) on staining with iodine vapor. No spot was observed that corresponded to isobarbituric acid (R_f 0.0). The spots corresponding to barbituric acid turned yellow on the paper.

The spots of the chromatograms that corresponded to barbituric acid were eluted with water and the ultraviolet spectra were observed. The spectra were consistent with barbituric acid in 0.01 *M* HCl, λ_{max} 257 mμ, and 0.01 *M* NaOH, λ_{max} 255 mμ.

Spectrophotometric pK'_a determinations at 23° were made on the degraded mixture of BU which is presumed to contain barbituric acid. The absorbance at 260 mμ plotted against pH indicated pK'_a values of 8.2 and 3.9. The former is assignable to BU with a known pK'_a of 8.1[4] and the latter is assignable to BA with a known pK'_a of 4.0.[17]

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