5-Arylthiopyrimidines. V. Kinetics of the Cyclization of 4-Oxo Derivatives to 10H- and 10-Alkylpyrimido[5,4-*b*][1,4]benzothiazines (1,3-Diazaphenothiazines)[1]

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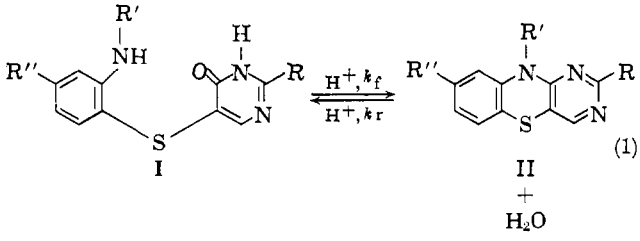
The kinetics of the acid-catalyzed cyclization of several pyrimidines of type I to pyrimidobenzothiazines of type II have been determined. Pyrimidines Ia, Ic, and Id, which have a 2-amino group, cyclized satisfactorily in 1 M hydrochloric acid at 94°. However, alkyl substitution on the anilino nitrogen, as in Ie and If, retards cyclization, probably for steric reasons, and favors side reactions. The dependence of Ia cyclization rate on temperature and acid concentration has been studied. The 2-oxopyrimidine Ib cyclized to the extent of only 15% in 1 M hydrochloric acid, but to a larger degree in alcoholic solvents and in moderately concentrated sulfuric acid solutions. It was established that cyclization of Ib attains a state of equilibrium. Rate and equilibrium constants have been measured as a function of medium composition, starting both from Ib and from the cyclization product IIb. Plots (ϕ-plots) of log k_f, log k_r and log ($[IIb \cdot H^+]/[Ib \cdot H^+]$) against (log $[H_2SO_4]$ + H_0) are linear for the reverse rate process, but the equilibrium and forward rate ϕ-plots show changes of slope at ca. 5 M sulfuric acid which are probably due to the incursion of a second stage of protonation of Ib. Preparations of several of the compounds studied are described.

The acid-catalyzed cyclization of 5-(*o*-aminoarylthio)pyrimidin-4-ones (I)[2] to 10H-pyrimido[5,4-*b*][1,4]benzothiazines (II) has recently been described.[3]



(1)

I ⇌ II + H_2O (H^+, k_f; H^+, k_r)

a, R = NH_2; R′, R″ = H
b, R = OH; R′, R″ = H
c, R = NH_2; R′ = H; R″ = Cl
d, R = $-N(CH_2)_5-$; R′ = H; R″ = Cl
e, R = NH_2; R′ = CH_3; R″ = H
f, R = NH_2; R′ = n-C_4H_9; R″ = H

Reactions of this type, which involve the intramolecular displacement of an oxo group from the pyrimidine 4-position, have not previously been described in the pyrimidine series. We have now studied the kinetics of this type of cyclization, with the object of determining the dependence of rate upon acidity, the relationship (if any) of such a dependence to the pK_a values for the protonation of the pyrimidines, and the effects of substituents on rate.

It was observed that the yield of cyclized product was strongly dependent on substituents in the pyrimidine ring. For example, the cyclization of Ia went virtually to completion in dilute aqueous acid, whereas Ib cyclized to only a small extent under similar conditions. In media of low water content the yield of IIb increased markedly, as would be expected if this were an equilibrium reaction. This is indeed the case. Rate measurements were carried out in both directions, and equilibrium constants were determined for the reaction Ib ⇄ IIb in various media.

As a synthetic method, this reaction appeared to offer a route to N[10]-alkylpyrimido[5,4-*b*][1,4]benzothiazines by cyclization of 5-(*o*-alkylaminophenylthio)pyrimidin-4-ones (Ie and If). It was found that *o*-alkylaminothiophenols could be condensed with 5-halopyrimidines to produce the desired intermediates (Ie and If), using methods previously described for *o*-aminothiophenols.[3] However, the yields of these thioethers showed a tendency to decrease as the size of the alkyl group R′ was increased. The *o*-alkylaminothiophenols used in these reactions were prepared from 3-alkyl-2-benzothiazolinones by fusion with potassium hydroxide, according to known techniques.

Treatment of 2-amino-5-(*o*-methylaminophenylthio)-pyrimidin-4-one (Ie) with 1 *M* hydrochloric acid in boiling ethanol produced the cyclized derivative IIe in 72% yield. When larger alkyl substituents were present, as with If, the cyclization proceeded only slowly and in poor yield. Evidence that the products of these reactions were 10-alkylpyrimidobenzothiazines of type II was obtained from their ultraviolet absorption spectra (Table VII), which were very similar in character to the spectra of the corresponding 10H-derivatives.[3] Alkylation produced only very slight changes in the major low wave length maximum at 240–243 mμ; the cations exhibited a bathochromic shift in the second smaller maximum in the 280-mμ region, and small shifts in the broad low maximum in the 360–390 mμ region of the spectrum. The kinetics of the cyclization of Ie and If were investigated to clarify the reaction rate differences.

Kinetic studies were carried out in aqueous hydrochloric acid media on all compounds (Ia–If). Additional media, described below, were employed with Ib and IIb. Rates were followed spectrophotometrically,

(1) A small section of this paper was presented at the 144th National Meeting of the American Chemical Society, Los Angeles, Calif., April 1963; see also Abstracts, XIXth Congress of the International Union of Pure and Applied Chemistry, London, 1963.

(2) These pyrimidinones are named according to the format in *Advan. Heterocyclic Chem.* 1, 315 (1963).

(3) B. Roth and L. A. Schloemer, *J. Org. Chem.*, **28**, 2659 (1963).

Table I. Rates of Cyclization of 5-(*o*-Aminoarylthio)pyrimidin-4-ones (I) to Pyrimido[5,4-*b*][1,4]benzothiazines (II) in Aqueous Hydrochloric Acid Solutions

Compd.	Pyrimidine 2-subst. (R)	R′	R″	Temp., °C.	[HCl], *M*	pH or H_0[a]	Cyclization at last point, %	$10^5 k_\psi$, sec.$^{-1}$
Ia	NH_2	H	H	62.2	0.988	−0.20	94	0.676
				74.05	0.988	−0.20	94	2.34
				84.1	0.988	−0.20	94	5.98
				94.1	0.0097	2.01	69.5	5.19
					0.0509	1.29	92	10.8
					0.097	1.01	94	12.5
					0.203	0.65	94	14.0
					0.599	0.10	94	14.7
					1.02	−0.20	92	14.1
					3.01	−1.05	80	9.9
Ic	NH_2	H	Cl	84.4	0.988	−0.20	94.5	11.4
				94.0	0.988	−0.20	94.5	27.4
Id	$-N(CH_2)_5-$	H	Cl	94.1	0.988	−0.20	91	20.6
Ie	NH_2	CH_3	H	94.1	0.203	0.65	56	1.35
					0.496	0.20	57	1.5[b]
					1.004	−0.20	51	1.4[b]
Ib	=O	H	H	84.1	0.988	−0.20	15	ca. 1.8

[a] For solutions having acidities greater than 0.1 *M*, the values of M. A. Paul and F. A. Long [*Chem. Rev.*, **57**, 1 (1957)] were used for the acidity function H_0. [b] k_ψ is the slope in plots of ln $(A_{\infty,exp} - A_t)$ *vs.* time, where $A_{\infty,exp}$ is the experimental infinity value. This decreased slowly with time, but no correction for product decomposition has been made.

with measurements being made at the long wave length maximum (between 350 and 420 mμ) of pyrimidobenzothiazines in acid solution. The arylthiopyrimidines do not absorb in this region. In all cases, the acid catalyst was present in large excess, and the kinetics were pseudo first order in the pyrimidine.

Results

Kinetic Studies. Rate coefficients for the cyclization of Ia–Ie in aqueous hydrochloric acid are shown in Table I. Rate coefficients for the cyclization of Ib in other solvent systems are shown in Tables II and IV. Rates for the solvolysis of IIb are found in Tables III and V. Details of the results are described below for each individual compound.

2-Amino-5-(o-aminophenylthio)pyrimidin-4-one (Ia). Determinations of the rate of cyclization as a function of acid concentration were carried out at 94.1°, at which temperature the rates could be conveniently measured. The rate was found to increase steadily up to about 0.6 *M* hydrochloric acid (H_0 = 0.1), where it went through a maximum and then decreased slowly. The data, found in Table I, are plotted in Figure 1. Measurements were not made at acidities greater than $H_0 = -1$ (3 *M* hydrochloric acid), because of evidence that the 2-amino group hydrolyzed to some extent at the higher acidities.

The yield also went through a maximum in the range of acidity of the rate maximum, and it was demonstrated in regions at and beyond the maximum that an equilibrium was present (see Experimental section). This equilibrium lies far to the right (92–94% cyclization) between 0.2 and 1 *M* hydrochloric acid. The reason the yield was only 69.5% at pH 2 was not established.

Rate measurements were carried out at three other temperatures in 0.988 *M* acid (Table I). The Arrhenius energy of activation, calculated from these data, is 23.3 kcal./mole, and the entropy of activation is −15 e.u.

2-Amino-5-(2-amino-4-chlorophenylthio)pyrimidin-4-one (Ic). The rate of cyclization of Ic was measured in 0.988 *M* acid only, at 84.4 and 94.0°. Difficulty was encountered at other acid concentrations because of insolubility of Ic and/or IIc. The effect of the *p*-halogen in the benzene ring was to increase the rate by about a factor of two. The extent of cyclization was not changed.

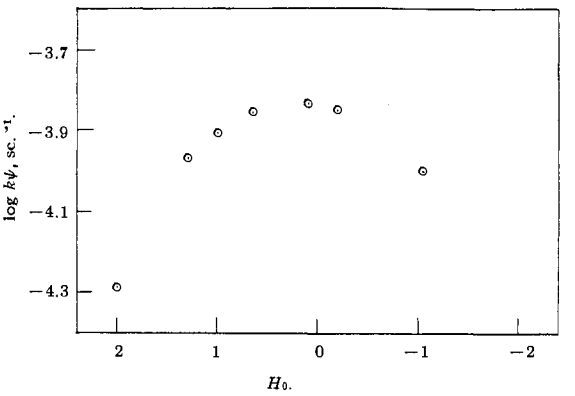


Figure 1. Rate of cyclization of 2-amino-5-(*o*-aminophenylthio)pyrimidin-4-one (Ia) as a function of acidity (hydrochloric acid, 94.0°).

5-(2-Amino-4-chlorophenylthio)-2-piperidinopyrimidin-4-one (Id). The rate of cyclization of Id, studied in 0.988 *M* acid only, was almost the same as that of the corresponding 2-amino derivative Ic, and the yield was similar. This substance also presented solubility problems at lower acid concentrations.

2-Amino-5-(o-methylaminophenylthio)pyrimidin-4-one (Ie). Kinetic experiments, carried out at three acidities, showed that the rate of cyclization went through a gentle maximum in about 0.5 *M* acid, as in the case of Ia. The results differed from those obtained with Ia in two important respects, however. First, the rate of cyclization of the methylamino compound was lower by a factor of ten, as might have been expected from steric considerations. Second, the reaction took more than one course. The maximum cyclization,

Table II. Rates of Cyclization of 5-(*o*-Aminophenylthio)pyrimidine-2,4-dione (Ib) to 10H-Pyrimido[5,4-*b*][1,4]benzothiazin-2-one (IIb) in Aqueous Sulfuric Acid Solutions at 84.2°[a]

Expt.	$[H_2SO_4]$, M	log $[H_2SO_4]$	H_0	log $[H_2SO_4] + H_0$	log a_{H_2O}	Cyclization at equil., %	[IIb]/[Ib]	log [IIb]/[Ib]	10^5k_{tot}, sec.$^{-1}$	10^5k_f, sec.$^{-1}$	log k_f	10^5k_r,[b] sec.$^{-1}$	log k_r
1	0.0642	−1.19	1.18	−0.01	...	(15.1)[c]	0.177	−0.728	11.5	1.74	−4.76	9.76	−4.01
2	0.694	−0.16	−0.03	−0.19	−0.009	16.4	0.196	−0.708	11.2	1.84	−4.74	9.36	−4.03
3	2.04	0.31	−0.86	−0.55	−0.044	23.2	0.302	−0.520	6.70	1.56	−4.81	5.14	−4.29
4	4.35	0.64	−2.00	−1.36	−0.165	41.5[d]	0.709	−0.149	2.40	0.995	−5.00	1.41	−4.85
5	5.09	0.71	−2.31	−1.60	−0.224	48.0[d]	0.924	−0.034	1.64	0.787	−5.10	0.853	−5.07
6	6.15	0.79	−2.84	−2.05	−0.335	54.3	1.19	0.076	0.901	0.489	−5.31	0.412	−5.39
7	7.39	0.87	−3.55	−2.68	−0.491	61.0	1.56	0.193	0.493	0.300	−5.52	0.193	−5.71
8	8.51	0.93	−4.15	−3.22	−0.671	67.5	2.08	0.318	0.215	0.145	−5.84	0.070	−6.16

[a] These solutions contained 2% ethanol, which was required to dissolve the compound. [b] By subtraction of k_f from k_{total}. [c] Product precipitated in the hot solutions before equilibrium was reached; total rate constant obtained by Guggenheim plots (E. Guggenheim, *Phil. Mag.*, **2**, 538 (1926); see A. Weissberger, "Technique of Organic Chemistry," Vol. VIII, Part 1, Interscience, New York, N. Y., 1961, pp. 135–136); k_f obtained by successive approximations of ∞ cyclization, until plot of log $(A_\infty - A_t)$ *vs.* time gave a straight line with slope matching the Guggenheim plot. [d] Corrected for slight decomposition.

Table III. Rates of Hydrolytic Ring Opening of 10H-Pyrimido[5,4-*b*][1,4]benzothiazin-2-one (IIb) in Aqueous Sulfuric Acid Solutions at 84.2°

Expt.	$[H_2SO_4]$, M	H_0	Hydrolysis at equil., %	10^5k_{tot}, sec.$^{-1}$	10^5k_r, sec.$^{-1}$	[IIb]/[Ib][a]
1	2.06	−0.89	77.0	6.75	5.20	0.300
2	4.35	−2.00	60.2	2.35	1.42	0.701

[a] Calculated from k_f (Table II)/k_r (this table).

which was 57%, does not represent an equilibrium value. When the reaction was carried out in the reverse direction in 0.5 *M* acid, only very slow decomposition occurred, to yield products other than Ie. Spectral examination of the residue remaining from the 57% cyclization indicated it to be a mixture of unidentified degradation products. These observations imply that N^{10}-substituted pyrimidobenzothiazines of this type are rather stable to acid hydrolysis once they are formed, but that their formation from substituted anilines is complicated by slower reaction rates and the formation of by-products.

2-Amino-5-[o-(n-butylamino)phenylthio]pyrimidin-4-one (If). Accurate rate measurements were not obtained on the cyclization of this compound because of competing reactions and the fact that it cyclized to only a small extent. There was marked curvature in the rate plot at 370 mμ, and the yield was only 13%.

5-(o-Aminophenylthio)pyrimidine-2,4-dione (Ib). The cyclization of Ib in 1 *M* hydrochloric acid proceeded only to the extent of 15% (Table I). This is in marked contrast with Ia, which was almost completely cyclized under these conditions. In 6 *M* hydrochloric acid, the yield was increased to about 25%.

Rate studies were then carried out in dilute and moderately concentrated sulfuric acid solutions, between 0.064 and 8.5 *M*. The data are shown in Table II. Measurements could not be made in solutions less acidic than pH 1 because of precipitation of the product in the hot solutions. The region of maximum rate was found to lie in the vicinity of 0.7 *M* acid ($H_0 = 0$).

The rate of cyclization decreased steadily with increasing acid concentration above 0.7 *M* sulfuric acid. The yield, on the other hand, steadily increased with increasing acid concentration, as the activity of water decreased. That this is a true equilibrium reaction was demonstrated by rate measurements on the reverse reaction. These are shown in Table III. The data of expt. 1 and 2, Table III, are to be compared with those of expt. 3 and 4, respectively, in Table II. Virtually identical equilibrium compositions were attained in both cases, and the total rates were also duplicated very closely. Side reactions are negligible.

Rate measurements were also carried out in ethanolic and methanolic hydrochloric or sulfuric acid solutions containing varying amounts of water (Tables IV and V). Only minor differences in forward rate occurred with varying water concentration, in approximately 1 *M* acid. The reverse rate changed to a greater extent, and the position of the equilibrium changed markedly, as might be expected upon decreasing the available water. The cyclization did not proceed beyond 77%, however, in ethanol containing only traces of water, and methanol was less effective than ethanol in favoring cyclization. These results suggested that alcoholysis of IIb was occurring in the essentially anhydrous alcohols, to produce 4-alkoxypyrimidines. Spectral shifts also indicated the presence of other components in the mixture, as did curvature in some of the rate plots (expt. 3, Table IV, for example). Experiment 1, Table V, illustrates a rate measurement in the reverse direction, to be compared with expt. 1, Table IV. The equilibrium positions agree in the two experiments; the approximately 20% difference between total rates ($k_f + k_r$) as measured from forward and reverse reactions probably represents experimental error and a small amount of by-product formation.

The reactions in ethanol are most useful for preparative purposes, since they provide a means for obtaining IIb in good yield in a reasonable time period. (Actually, the yield in preparative experiments was better than the results here might suggest, since IIb precipitated from the reaction mixture in the more concentrated solutions, thus allowing the reaction to go more nearly to comple-

Table IV. Rates of Cyclization of 5-(*o*-Aminophenylthio)pyrimidine-2,4-dione (Ib) to 10H-Pyrimido[5,4-*b*][1,4]benzothiazin-2-one (IIb) in Various Solvent Systems Containing Mineral Acid at 84.2°.

Expt.	Acid, *M*	Solvent	Water, % (vol.)	Cyclization at equil., %	10^5k_{tot}, sec.$^{-1}$	10^5k_f, sec.$^{-1}$	10^5k_r,[a] sec.$^{-1}$	K[b]
1	HCl, 0.956	EtOH	52.4	27.1	12.	3.3	8.8	0.372
2	HCl, 0.998	EtOH	12.7	66.2	9.5	6.3	3.2	1.96
3	HCl, 0.889	EtOH	0.09	77.0	7.8[c]	6.0	1.8	3.35
4	HCl, 0.960	CH_3OH	7.4[d]	46.5	9.2	4.3	4.9	0.87
5	H_2SO_4, 2.67	EtOH	13	76.2	7.7	5.9	1.8	3.20
6	H_2SO_4, 0.290	EtOH	13	...[e]	...	...	...	...
7	HCl, 1.006	CH_3COOH	5.9[d]	75.5	0.64	0.49	0.15	3.08

[a] By subtraction of k_f from the rate constant for the total reaction (k_{tot}). [b] Apparent equilibrium constant, ([IIb]/[Ib]). [c] Log $(A_\infty - A_t)$ *vs.* *t* curved after 50% reaction. [d] By weight. [e] Complete decomposition of product. Optical density, 415 mμ, increased from 0 to a maximum of 0.344 (40.5% of theory) in 6 hr., and then decreased to 0 during 72 hr. (see Table V also).

Table V. Rates of Solvolytic Ring Opening of 10H-Pyrimido[5,4-*b*][1,4]benzothiazin-2-one (IIb) in Alcoholic Systems Containing Mineral Acid at 84.2°

Expt.	Acid, *M*	Solvent	Water, % (vol.)	Solvolysis at equil., %	10^5k_{tot}, sec.$^{-1}$	10^5k_r,[a] sec.$^{-1}$	K[b]
1	HCl, 0.956	EtOH	52.4	73.0	9.7	7.1	0.46
2	H_2SO_4, 0.290	EtOH	13	...[c]	*ca.* 4.5[d]	...	...

[a] k_r here refers to the reaction IIb → Ib. [b] Apparent equilibrium constant, calculated from k_f (Table IV)/k_r (this table). [c] Complete decomposition to a new substance, identical in spectrum with that obtained in Table IV, expt. 6, and different from Ib. [d] Plot of log $(A_\infty - A_t)$ gave a straight line with some scatter. Accuracy was prevented by rapid precipitation of IIb on cooling, in the case of the initial samples.

tion.) Although cyclization has been shown to occur in relatively high yield in 7–9 *M* aqueous sulfuric acid solutions, the rates are very low and these media are unattractive for preparative work.

When the acid concentration was less than about 0.5 *M* in dilute alcoholic solutions, formation of IIb was followed by a second reaction, in which the characteristic long wave length peak of IIb gradually disappeared. This occurred at acid concentrations such that IIb was not completely monoprotonated, as shown by the fact that λ_{max} was below 410 mμ (λ_{max} for the nonprotonated species is at 375 mμ). The proposition that IIb was actually formed as a transitory intermediate is supported by the fact that IIb behaved in the same manner when treated with dilute alcoholic acid (see Table IV, expt. 6, and Table V, expt. 2). This phenomenon was not observable in aqueous medium because of the insolubility of IIb. Table IV, expt. 5, demonstrates that this phenomenon does not occur in stronger alcoholic sulfuric acid.

The molarities of acids shown in Tables IV and V represent initial concentrations. Some acidity was lost during the heating period through reaction of the acid with the solvent. A reaction was carried out with hydrochloric acid in acetic acid, where this loss in acidity would not be expected to occur (Table IV, expt. 7). Although 75% cyclization occurred, the reaction was so slow that this type of medium was abandoned.

pK_a Studies. Determination of the pK_a values of the arylthiopyrimidine reactants is discussed in part IV of this series,[4] where it was shown that the derivatives possessing amino or alkylamino groups in both rings undergo diprotonation, and that the two stages of protonation overlap. The uracil derivative Ib, on the other hand, became monoprotonated at the anilino nitrogen only, in the pH range 0–6. The basicity of uracil and its derivatives has been investigated by Katritzky and Waring[5] by spectrophotometric means in sulfuric acid solutions. They reported values of −3.38 and −7.25 for uracil and 5-bromouracil, respectively, and judged that the compounds were not Hammett bases on the basis that graphs of log ([S]/[SH$^+$]) against H_0 gave straight lines which did not have unit gradient.

We investigated the spectra of 5-phenylthiopyrimidine-2,4-dione (5-phenylthiouracil), its *o*-amino derivative Ib, and the isocytosine analog Ia in sulfuric acid solutions between H_0 values of 0 and −10.[6] Figure 2 shows the spectra of 5-phenylthiouracil in various media. The changes in spectrum that occur

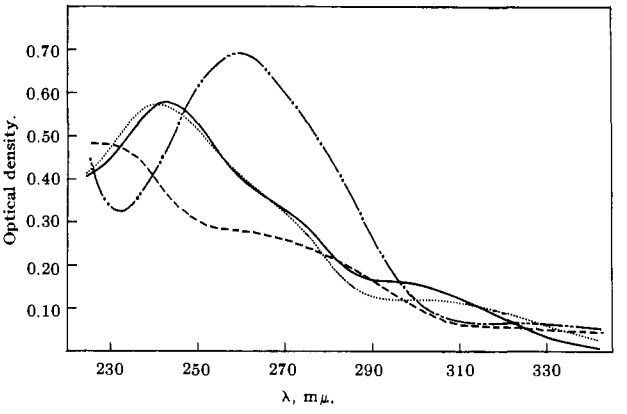


Figure 2. Ultraviolet absorption spectra of 5-phenylthiouracil and its reaction products in sulfuric acid: ———, pH 1; · · ·, H_0 = −4.4; – – –, H_0 = −8.0; — · · — · · —, H_0 = −10.

with this substance in sulfuric acid are not simple. Between pH 1 and H_0 −4 there is only a small decrease in optical density in the 290-mμ region of the spectrum

(4) B. Roth and J. F. Bunnett, *J. Am. Chem. Soc.*, 87, 334 (1965).

(5) A. R. Katritzky and A. J. Waring, *J. Chem. Soc.*, 1540 (1962).

(6) Data of M. J. Jorgenson and D. R. Hartter [*J. Am. Chem. Soc.*, 85, 878 (1963)] were used for the upper sulfuric acid region.

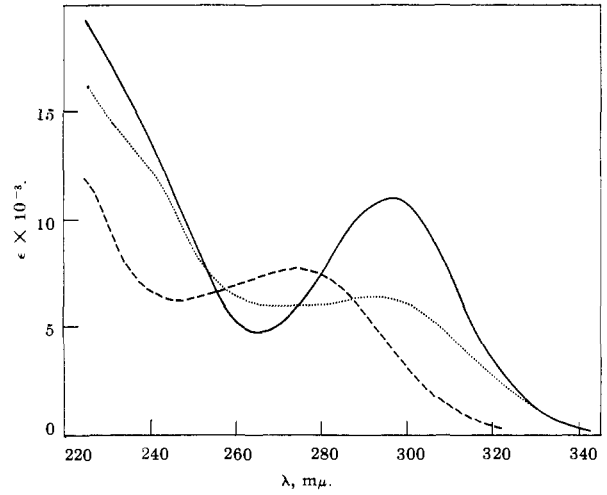


Figure 3. Ultraviolet absorption spectra of 5-(*o*-aminophenylthio)-pyrimidine-2,4-dione: · · ·, neutral species; – – –, monoprotonated species; ———, monoanionic species.

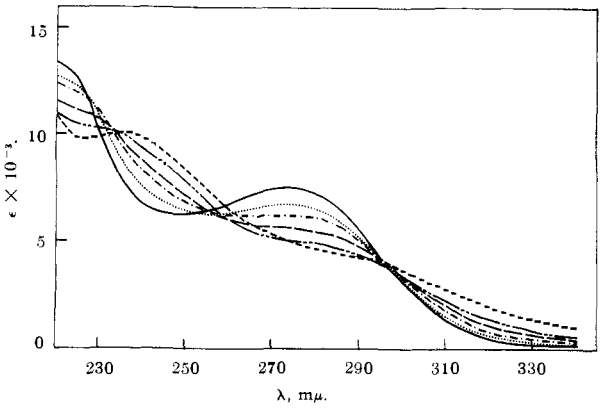


Figure 4. Ultraviolet absorption spectra of 5-(*o*-aminophenylthio)pyrimidine-2,4-dione in sulfuric acid solutions: ———, H_0 = −2.0; · · ·, H_0 = −5.7; – · – · –, H_0 = −6.8; – – –, H_0 = −7.5; — · · — · ·, H_0 = −8.2; ·····, H_0 = −10.

and a very slight hypsochromic shift below 240 mμ. Between −4 and −8 there is a more pronounced decrease in optical density in the 240-mμ region, which is accompanied by a hypsochromic shift in the low wave length maximum. At higher acidities the molecule very rapidly becomes sulfonated, probably in the *para* position of the benzene ring. This causes a pronounced bathochromic and hyperchromic shift of the lower wave length maximum to 259 mμ in concentrated sulfuric acid. The new spectral characteristics are maintained on dilution of the acid (see Experimental section for characterization of the product). Such facts do not allow easy assignment of dissociation constants for the original protonated base.

The spectra of Ib were less complex in that there was no evidence of sulfonation under these conditions. Figure 3 shows the spectra of the neutral, anionic, and monocationic species. The spectrum is virtually unchanged between 1 and 4.5 *M* sulfuric acid, but then alters as the acid becomes more concentrated. Figure 4 depicts the relatively small changes that occur in 4.5–18 *M* sulfuric acid. A continuous decrease in extinction occurs in the 275-mμ region between H_0 values of −2 and −8, whereas similar increases in absorption take place at 240 and above 300 mμ over a range extending to at least −10 on the H_0 scale. An isosbestic point is very nearly defined at 297.5 mμ, but large deviations occur at the two other crossover regions. The spread of changes suggests phenomena which are more complex than those involved with the addition of one proton to the uracil moiety. Thus we do not wish at this time to assign a single pK_a value for the protonation of the pyrimidine (although a value of approximately −6.1 may be reached by using the treatment of Katritzky and Waring[5]). This subject will be discussed in greater detail in a future paper which shows greater spectral differences of related pyrimidines.

Compound Ia exhibited spectral changes in acid which were qualitatively similar to those observed with Ib; however, the magnitude of change was considerably less than with Ib. The relatively large experimental error in this case renders quantitative interpretation difficult.

The constants representing the monoprotonation of some of the pyrimidobenzothiazines discussed here were also determined spectrophotometrically, and were routine with the exception of IIb, which is too insoluble in aqueous medium for determination of the spectrum of the neutral species. However, the partially protonated molecule remains soluble, thus rendering it possible to estimate the pK_a from the portion of the sigmoid curve which can be obtained by plotting the difference in optical density at two wave lengths against the pH. These pK_a values are recorded in Table VI.

Table VI. Basic pK_a Values for Pyrimidobenzothiazines[a]

Compd.	pK_a
IIa	5.61[b]
IIb	1.6[c]
IIe	5.58
IIf	5.61

[a] ±0.05 pH unit. [b] See ref. 3. [c] Approximate; see text.

Discussion

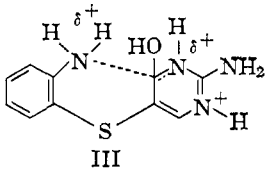
2-Amino Derivatives Ia, Ic, Id, Ie, and If. The rate of cyclization of Ia in aqueous solution experiences a gentle maximum in *ca.* 0.6 *M* hydrochloric acid (Table I). This is approximately the acid concentration at which transformation of Ia to its diprotonated form (which has pK_a = 2.1 ± 0.2[4]) is 99% complete. The depression of rate caused by further increase in acid concentration can be attributed, if water molecules are required to form the cyclization transition state, to the lowering of the activity of water at higher acid concentrations.[7]

From the point of view of collision theory, it seems unlikely that the reactive form of diprotonated Ia has one proton on each basic moiety (the aminopyrimidone system and the anilino nitrogen). A much more reactive tautomer would be that accommodating both protons in the pyrimidine system. Such a proton disposition would maximize the nucleophilic reactivity of the anilino nitrogen and the electrophilic reactivity of the pyrimidine 4-position.

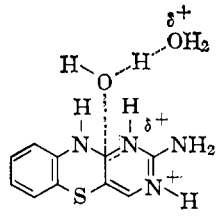
With reference to transition state theory, one cannot specify which atoms will bear protons in the transition state. Presumably the present transformation, like

(7) J. F. Bunnett, *J. Am. Chem. Soc.*, **83**, 4956, 4968, 4973, 4978 (1961).

most nucleophilic substitutions at unsaturated carbon, is a multi-step reaction[8]; one cannot even say which step represents the highest peak on the energy profile of the reaction. If forming the new C–N bond is rate limiting, the transition state perhaps resembles III. If expulsion of the 4-hydroxy group is the crucial step, general acid catalysis may be involved, in which case a transition state like IV is conceivable.



III



IV

The dependence of the state of equilibrium between Ia and IIa on hydrochloric acid concentration is governed by the degrees of protonation of the predominant forms of these two species and by the medium dependence of their activity coefficients. The latter factor depends to a large extent on the amount of hydration of Ia and IIa.[7] In view of the larger number of hydrogen-bearing functional groups in Ia than in IIa and the fact that a molecule of water is released from covalent binding on formation of IIa, it is likely that at equal levels of protonation the equilibrium would shift toward IIa as acid concentration increased above 0.5 *M*.

The equilibrium actually shifts toward Ia (Table I). This fact is consonant with evidence that Ia is diprotonated in this acid concentration range, while IIa is monoprotonated. The equilibrium should be written (in formal notation)

$$\text{Ia}\cdot 2\text{H}^+ \rightleftharpoons \text{IIa}\cdot\text{H}^+ + \text{H}^+ + \text{H}_2\text{O} \qquad (2)$$

The tendency of higher acid concentration to shift the equilibrium to the left is doubtless partially mitigated by the activity coefficient factor mentioned above.

The fact that Ic cyclizes about twice as fast as Ia in 0.988 *M* hydrochloric acid at 94° might seem strange inasmuch as the chlorine atom should reduce the nucleophilicity of the anilino nitrogen. That factor is doubtless more than offset by a more favorable disposition of protons among the various tautomers of diprotonated Ic. A reasonable estimate is that the population of tautomers having both protons associated with the pyrimidine moiety is five times greater than in diprotonated Ia.[9] Alternatively, one can paraphase the facts by saying that the introduction of a chlorine atom adds more to the free energy of diprotonated Ia than of a transition state such as III or IV. This is reasonable, for in the predominant form of diprotonated Ia or Ic the anilino nitrogen bears a full positive charge while in transition states III and IV it carries at most a partial positive charge.

The low cyclization rates of Ie and If can be attributed to steric hindrance. Nucleophilic substitutions at unsaturated carbon are known to be quite sensitive to the size of the attacking nucleophile.[10] Speculation on the nature of the side reaction(s) with these two substrates is not warranted.

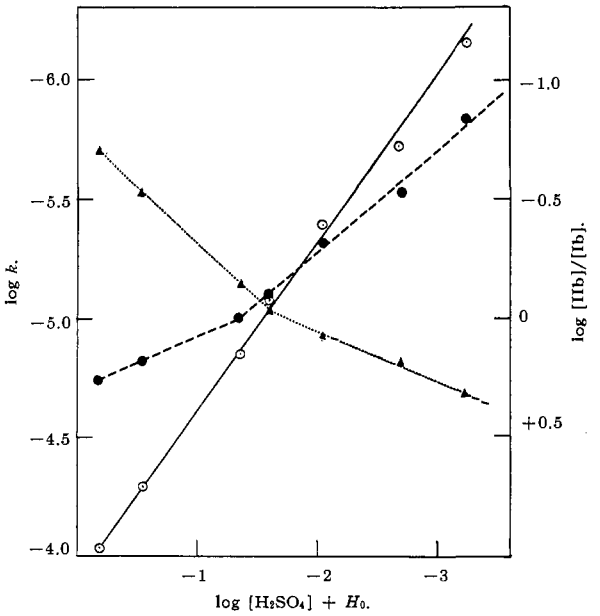


Figure 5. ϕ-Plots for cyclization of Ib, hydrolytic ring opening of IIb, and equilibria in 0.7–8.5 *M* sulfuric acid: solid circles and dashed line for k_f; open circles and solid line for k_r; triangles and dotted line for K_e.

The 2-Oxo Compound (Ib). Evidence is that both Ib and IIb are monoprotonated in *ca.* 1 *M* sulfuric acid. Accordingly, the data in Table II, concerning the dependence of the Ib $\rightleftharpoons$ IIb equilibrium and of the rates of the forward and reverse reactions on acid concentration, may be analyzed in terms of ϕ- and w'-values,[11] both Ib and IIb being treated as "strongly basic" substrates. In this type of analysis, plots of log ([IIb·H$^+$]/[Ib·H$^+$]), log k_f and k_r, respectively, against log ([H_2SO_4] + H_0) are constructed. Ordinarily, in the absence of complicating factors, such plots are straight. Their slopes constitute ϕ-values, which are parameters useful for characterizing the dependence of rate or equilibrium on acid concentration. A subsidiary parameter, w', defined as 4.5ϕ, is preferred for purposes of discussion.

The plots are presented in Figure 5. Actually, only that for the reverse rate process is linear as anticipated. The plots for the forward rate process and the equilibrium reaction are each composed of two linear segments with a break in the middle.

The equilibrium is concerned with relationships between Ib and IIb, while the forward and reverse rates concern relationships between each of these species and the transition state. Because the ϕ-plot based on reverse reaction rate is linear, we judge that the activity coefficient ratio, $f_{\text{IIb}\cdot\text{H}^+}/f_{\pm\text{H}^+}$, behaves "normally." Since both the equilibrium and the forward rate ϕ-plots are bent, and these both concern the concentration and activity coefficient of Ib·H$^+$, we deduce that Ib·H$^+$

(8) J. F. Bunnett, "Theoretical Organic Chemistry: Proceedings of the Kekulé Symposium," Butterworth and Co. (Publishers) Ltd., London, 1959, p. 144; M. L. Bender, *Chem. Rev.*, 60, 53 (1960).

(9) This estimate takes account of the Hammett σ-value of *p*-Cl (+0.23) and the ρ-values for anilinium ion dissociation (*ca.* +3); H. H. Jaffé, *ibid.*, 53, 191 (1953).

(10) (a) R. Baltzly, I. M. Berger, and A. A. Rothstein, *J. Am. Chem. Soc.*, 72, 4149 (1950); (b) J. F. Bunnett and R. E. Zahler, *Chem. Rev.*, 49, 273 (1951).

(11) J. F. Bunnett and F. P Olsen, Abstracts, 145th National Meeting of the American Chemical Society, New York, N. Y., Sept. 1963, p. 41Q.

somehow behaves "abnormally" as the acid concentration changes.

In sulfuric acid more concentrated than 5 *M*, the breaks in the forward rate and equilibrium ϕ-plots are both in the direction of lesser reactivity for $Ib \cdot H^+$ than is extrapolated from its behavior in less concentrated acid. This suggests either that the concentration of $Ib \cdot H^+$ begins to diminish at or about the break, or that its activity coefficient depends irregularly on acid concentration. A change in the concentration of $Ib \cdot H^+$ could be caused by its conversion to a diprotonated form. Inasmuch as the spectrum of Ib in moderately concentrated sulfuric acid solutions (see above) begins to change at approximately the acid concentration at which the break in Figure 5 occurs, it seems probable that the break is due to inception of a second stage of protonation of Ib.

This line of reasoning implies that diprotonated Ib is relatively unreactive in cyclization. The activation energy to the diprotonated transition state appears to be much higher than from monoprotonated Ib to monoprotonated transition state. According to transition state concepts, one should also consider the "equilibrium" between diprotonated Ib and a transition state with one less proton

$$Ib \cdot 2H^{+2} \rightleftharpoons \ddagger \cdot H^+ + H^+ \qquad (3)$$

However, this would probably be shifted to the left by increasing acid concentration just as equilibrium 2 is, and as the equilibrium between $Ib \cdot 2H^{+2}$ and $IIb \cdot H^+$ appears to be.

Because of the apparent intrusion of diprotonation of Ib at about 5 *M* sulfuric acid, interpretation of the ϕ- or w'-values for the equilibrium and forward rate processes is best confined to the 0.7–5 *M* region.

For the reverse reaction, ϕ is +0.71 and w' (4.5ϕ) is +3.2. This magnitude indicates that water acts as a proton transfer agent in the slow step. Many other reactions of hydrolysis at unsaturated carbon have similar w'-values.[11]

On the dilute side of the break, ϕ for the forward reaction is +0.22 and w' is +1.0. On the hypothesis that differences in degrees of hydration largely determine differences in activity coefficients in such systems,[7] this implies that the increase in hydration in going from $Ib \cdot H^+$ to transition state is on the average about 2.2 water molecules less than in going from $IIb \cdot H^+$ to (the same) transition state. One of these should be that released from covalent binding in the forward reaction, and the other 1.2 molecules the average amount by which water solvation of $Ib \cdot H^+$ exceeds that of $IIb \cdot H^+$. Inasmuch as monoprotonated Ib has five nitrogen or oxygen atoms bearing a total of five protons, while $IIb \cdot H^+$ has but four nitrogen or oxygen atoms bearing a total of three protons, it is reasonable that $Ib \cdot H^+$ should be the more solvated.

For the equilibrium, $Ib \cdot H^+ \rightleftarrows IIb \cdot H^+ + H_2O$, the slope ($\phi$) in Figure 5 below 5 *M* is −0.48 and w' is −2.1.

Experimental[12]

2-Amino-5-(o-aminophenylthio)pyrimidin-4-one (*Ia*), prepared as in Part III of this series,[3] was purified by repeated crystallization from 2-methoxyethanol, and also from 80% ethanol. The physical data were unchanged from those previously recorded.[3]

5-(o-Aminophenylthio)pyrimidine-2,4-dione (*Ib*)[3] was purified as for Ia. This served to remove a trace of color, but did not otherwise alter the physical constants previously reported.[3]

2-Amino-5-(o-methylaminophenylthio)pyrimidin-4-one (*Ie*). A mixture of 10 g. (0.0606 mole) of 3-methyl-2-benzothiazolinone[13] and 22 g. of potassium hydroxide pellets was heated in an iron vessel to the fusion point (oil bath 220°), and held there for 10 min. After cooling, the mixture was dissolved in water, neutralized with acetic acid, and extracted with ether. Titration of an aliquot of the dried (Drierite) ethereal extracts with iodine indicated the presence of 0.055 mole of 2-methylaminothiophenol. Upon removal of the solvent, a yellow oil remained. This was mixed with 100 ml. of ethylene glycol, 10.5 g. (0.055 mole) of 5-bromoisocytosine, and 7.6 g. (0.055 mole) of potassium carbonate, and was heated under nitrogen to 140° for 2 hr. A clear solution was formed, from which an oily layer separated on cooling. The mixture was poured into water and extracted with ether to remove any diaryl disulfide. Upon neutralization of the aqueous solution with acetic acid, a cream-colored precipitate separated. This was isolated and reprecipitated from alkali, which yielded 6.1 g. (44%) of Ie. Upon recrystallization from 50% ethanol, the compound was obtained as a hydrate melting at 237–239°.

Anal. Calcd. for $C_{11}H_{12}N_4OS \cdot H_2O$: C, 49.61; H, 5.30; N, 21.04. Found: C, 49.23; H, 5.08; N, 21.30.

Recrystallization from 95% ethanol, in which the substance was sparingly soluble, produced white crystals melting at 245–246° dec.

Anal. Calcd. for $C_{11}H_{12}N_4OS$: C, 53.21; H, 4.87; N, 22.57. Found: C, 53.27; H, 5.27; N, 22.60.

2-Amino-10-methylpyrimido[5,4-b][1,4]benzothiazine (*IIe*). A mixture of 1.0 g. (0.004 mole) of 2-amino-5-(*o*-methylaminophenylthio)pyrimidin-4-one, 20 ml. of ethanol, and 2 ml. (0.024 mole) of concentrated hydrochloric acid was heated under reflux for 12 hr. Upon chilling, yellow crystals separated, yielding 0.58 g. This product was very soluble in water. Upon addition of sodium hydroxide, a gum precipitated which soon solidified (0.50 g.). An additional 0.17 g. was obtained by adding water and alkali to the original alcoholic filtrate (total, 72%). The combined precipitates were recrystallized twice from ethanol, which yielded pale yellow plates, m.p. 192–194°.

Anal. Calcd. for $C_{11}H_{10}N_4S$: C, 57.37; H, 4.38; N, 24.33. Found: C, 57.71; H, 4.34; N, 24.47.

2-Amino-5-(o-n-butylaminophenylthio)pyrimidin-4-one (*If*). 3-(*n*-Butyl)-2-benzothiazolinone[14] (17.1 g., 0.082 mole) was fused with potassium hydroxide in the manner described for Ie to produce 2-(*n*-butylamino)thiophenol. This product (0.064 mole) was heated with 12 g. (0.063 mole) of 5-bromoisocytosine and 9 g. (0.065 mole) of potassium carbonate in 120 ml. of ethylene glycol at 150–160° for 3 hr. under nitrogen. The product was isolated as described for Ie yielding

(12) Melting points are corrected, and were carried out for the most part on a hot-stage microscope; melting points above 300° were carried out on a National Instrument Co. Melt-Meter.

(13) K. Fujii, *J. Pharm. Soc. Japan*, 77, 3 (1957); *Chem. Abstr.*, **51**, 8756 (1957).

(14) K. Tsuda and S. Oguri, *J. Pharm. Soc. Japan*, **62**, 66 (1942); *Chem Abstr.*, **45**, 1580 (1951).

5.82 g. (32%). After three recrystallizations from ethanol, the white product melted at 176–178°.

Anal. Calcd. for $C_{14}H_{18}N_4OS$: C, 57.90; H, 6.25; N, 19.29. Found: C, 57.42; H, 6.51; N, 19.58.

2-Amino-10-(n-butyl)pyrimido[5,4-b][1,4]benzothiazine Hydrochloride (IIf). One gram of If was treated with hydrochloric acid in ethanol in the manner employed for IIe. After 16 hr., the products were isolated. There was recovered 0.79 g. of alkali-soluble material (If), plus 0.15 g. of a yellow hydrochloride (alkali-insoluble). The reaction was repeated for 90 hr. using the recovered If. Again alkali-soluble material was recovered (0.38 g.), which proved to be a mixture in which the 2-amino group of If was partially hydrolyzed, as judged by analysis (Found: C, 57.97; H, 6.14; N, 15.73) and spectral characteristics. An alkali-insoluble oil was formed, which yielded a yellow hydrochloride (0.22 g.) upon treatment with ethereal hydrogen chloride. This was purified by recrystallization from ethanol, m.p. 212–214° (IIf).

Anal. Calcd. for $C_{14}H_{16}N_4S \cdot HCl$: C, 54.44; H, 5.55; Cl, 11.48; N, 18.14. Found: C, 54.22; H, 5.52; Cl, 11.87; N, 18.44.

5-Phenylthiopyrimidine-2,4-dione. A mixture of 3.66 g. (0.025 mole) of 5-chlorouracil, 3.3 g. (0.03 mole) of thiophenol, 3.45 g. (0.025 mole) of potassium carbonate, and 40 ml. of ethylene glycol was heated to 130–140° for 2 hr. A clear solution was formed, which solidified to a white crystalline mass upon cooling. This was dissolved in 200 ml. of dilute sodium hydroxide solution, and clarified from a slight cloudiness with the aid of diatomaceous earth. Upon neutralization with acetic acid, a white precipitate formed, which was isolated and extracted with acetone and ether to remove residual mercaptan and disulfide. The remaining solid weighed 3.70 g. (67% as 5-phenylthiopyrimidine-2,4-dione), and melted at 270.5–272°. After two recrystallizations from 2-methoxyethanol, the product melted at 272°.

Anal. Calcd. for $C_{10}H_8N_2O_2S$: C, 54.53; H, 3.66; N, 12.72. Found: C, 54.65; H, 4.15; N, 12.57.

When this reaction was carried out in a similar manner, but using 5-bromouracil in place of 5-chlorouracil, the yield of the 5-phenylthiopyrimidine was only 11%. Uracil was formed as a major product.

Sodium 5-(p-Sulfophenylthio)pyrimidine-2,4-dione. A solution of 0.50 g. of 5-phenylthiopyrimidine-2,4-dione in 1.5 ml. of concentrated sulfuric acid was allowed to stand at room temperature for 22 hr. A reddish color developed. The solution was then diluted with ice to a volume of 5.7 ml. Solid sodium carbonate monohydrate (0.96 g.) was then added slowly until a crystalline precipitate (A) separated in the still strongly acid medium; weight 0.42 g. Upon neutralization of the filtrate, which required 2.38 g. of additional sodium carbonate, a further 0.51 g. of white solid (B) separated. Both solids were very soluble in water and qualitatively had the same ultraviolet absorption maxima. Fraction A was recrystallized from 4.5 *M* sulfuric acid, and then thoroughly washed with ethanol.

Anal. Calcd. for $C_{10}H_7N_2NaO_5S_2$: C, 37.26; H, 2.19; N, 8.69; Na, 7.13. Found: (A) C, 36.62; H, 2.53; N, 8.20; Na, 6.7.

Fraction B was recrystallized several times from 50% ethanol, but sodium sulfate was retained in the crystals.

Anal. Calcd. for $C_{10}H_7N_2NaO_5S_2 \cdot 0.4Na_2SO_4 \cdot H_2O$: C, 30.24; H, 2.28; N, 7.06; Na, 10.42; S, 19.38. Found: (B) C, 29.66; H, 2.2; N, 6.90; Na, 10.2; S, 19.01.

The product A was found to have a single pK_a of 8.24 (±0.05) in the pH range 0–12. The substance had ultraviolet absorption maxima, mμ ($\epsilon \times 10^{-3}$), at: λ_{max} (0.1 *N* HCl), 257 (18.8) and sh 300 (4.9); λ_{min} 230 (7.8); λ_{max} (pH 11.0, glycine–sodium hydroxide) 261 (14.9) and 290 (14.2); λ_{min} 230 (10.9), 275 (13.2). Isosbestic points occurred at 241 and 270 mμ.

2-Amino-5-phenylthiopyrimidin-4-one was prepared as previously described.[15] It was purified by recrystallization from 2-methoxyethanol and from 95% ethanol, which did not change the melting point from that originally reported. The compound was found to undergo a photochemical reaction very rapidly when dissolved in ethanol and exposed to sunlight. The nature of this reaction will be described elsewhere.

o-Phenylthioaniline. *o*-Chloronitrobenzene was treated with thiophenol to produce 1-nitro-2-phenylthiobenzene, m.p. 69–70°, which was reduced as described by Mauthner[16] to produce *o*-phenylthioaniline. This product was purified by fractional distillation, b.p. 183° (11 mm.).

Ultraviolet Absorption Spectra and pK_a Determinations. Ultraviolet spectral determinations were carried out with a Beckman DU spectrophotometer. Methods used for the determination of pK_a values between 0 and 14 are described in part III of this series.[3] Measurements in strong sulfuric acid solutions were carried out by dissolving the compound at a concentration of 25 mg./10 ml. of appropriate solvent (usually 0.06 *M* sulfuric acid containing a little ethanol), followed by a 250-fold dilution into the sulfuric acid. The concentrations of the sulfuric acid solutions were determined from the densities (20°). Ultraviolet spectral characteristics of the N^{10}-alkylpyrimidobenzothiazines and their intermediates are described in Table VII.

Kinetic Procedure. Solutions were prepared by dissolving weighed amounts of the appropriate pyrimidines in standard acids. Usually twelve to fourteen 3-ml. aliquots were placed in 10-ml. flint glass "Color-break" flat-bottomed ampoules,[17] which were sealed and placed simultaneously in the thermostat. Individual ampoules were removed at recorded times and plunged into ice–water. One-ml. portions were removed and diluted to 10 ml. usually with the corresponding acid at a concentration of 0.1 *N*. The optical densities (A_t) were then read with a Beckman DU spectrophotometer at the long wave length maximum (between 370 and 420 mμ) for each pyrimidobenzothiazine in question. The 5-arylthiopyrimidines do not absorb in this region.

"Infinity" ampoules were removed after at least eight half-lives, and were normally run in duplicate to obtain the "infinity" optical densities (A_∞). Plots of log ($A_\infty - A_t$) *vs.* time were linear to 80–90% of reaction in practically all cases. The slopes were multiplied by −2.30 to obtain the k_ψ values for the total reaction

(15) B. Roth and G. H. Hitchings, *J. Org. Chem.*, **26**, 2770 (1961).
(16) F. Mauthner, *Ber.*, **39**, 3597 (1906).
(17) Kimball Glass Co.; these showed no tendency toward breakage, even when heated as high as 170° with dilute hydrochloric acid solutions, and were very convenient.

Table VII. Ultraviolet Absorption Spectra of 10-Alkylpyrimidobenzothiazines and 5-Arylthiopyrimidine Intermediates

Compd.	Cation				Neutral species				Anion			
	λ_{max}, mμ	ε × 10^{-3}	λ_{min}, mμ	ε × 10^{-3}	λ_{max}, mμ	ε × 10^{-3}	λ_{min}, mμ	ε × 10^{-3}	λ_{max}, mμ	ε × 10^{-3}	λ_{min}, mμ	ε × 10^{-3}
IIe	241	32.6	266	14.7	243	29.6	285	2.1	...		...	
	271	15.2	335	2.4	313	6.0						
	280 sh	13.4			350 sh	5.3						
	300 sh	4.9										
	367.5	3.50										
IIf	242	35.8	267	15.1	243	29.0	287	2.6	...		...	
	272	15.8	338	2.16	312	4.9						
	280 sh	14.4			350 sh	3.7						
	300 sh	5.3										
	377	3.46										
Ie	230 sh	10.9	270	7.7	240 sh	15.7	272	5.6	240 sh	16.4	272	7.1
	282	7.8			301	9.3			292	9.4		
If	230 sh	9.9							243	12.9	275	5.7
	275 sh	6.6			—		—		297	7.3		

(k_{tot}). In a number of instances the reactions were carried out in both directions, *i.e.*, starting with the open-chain arylthiopyrimidine in one instance, and with the tricyclic pyrimidobenzothiazine in the other, using otherwise identical conditions. The "infinity" optical densities were virtually identical, and the slopes of the plots of log $(A_\infty - A_t)$ *vs.* time were very similar starting in either direction. In such a case, $k_{tot} = k_f + k_r$, where k_f and k_r are pseudo-first-order rate coefficients for the forward and reverse reactions, respectively.[18] The rate constants k_f and k_r were then reckoned from this and the relationship, k_f/k_{tot} = fractional yield = $A_\infty/A_{\infty,theo}$, where A_∞ is the experimental infinity absorbance and $A_{\infty,theo}$ is the infinity absorbance computed from the extinction coefficients of the products on the assumption of 100% cyclization. The equilibrium constant, K, was evaluated as k_f/k_r or as $A_\infty/(A_{\infty,theo} - A_\infty)$.

Thermostat temperatures generally varied ±0.1°; in the region above 90° the variations were sometimes ±0.2°.

Rate Measurements on Cyclization of Ia. Kinetic runs were carried out in aqueous hydrochloric acid between 0.01 and 3 *N*. The concentration of pyrimidine was 1.707×10^{-3} *M* in all experiments. Solutions were diluted 1:10 into 0.1 *N* hydrochloric acid for spectral readings, which were recorded between 300 and 400 mμ. The optical densities at 385 mμ (λ_{max}) were used for A_t values (ε 3370 for IIa, and 0 for Ia). Detail on a typical run is presented in Table VIII.

The plot of log $(A_\infty - A_t)$ *vs.* time was strictly linear through 240 min., with slope -6.79×10^{-5} sec.$^{-1}$; k_{tot} is then 1.56×10^{-4} sec.$^{-1}$. The yield is (0.541/0.575) × 100 = 94.2%. Then k_f is 1.47×10^{-4} sec.$^{-1}$.

Stability of IIa in 3 N Hydrochloric Acid. A 36.9-mg. portion of IIa (free base) was dissolved in 100 ml. of 3 *N* hydrochloric acid. Heat was required to effect solution. This resulted in an apparent decrease in optical density from 0.575 (calcd.) to 0.552 (found) (1:10 dilution), at 385 mμ. Aliquots (3 ml.) were placed in ampoules, sealed, and heated at 94.0°. The change in optical density (385 mμ) with time (1:10 dilution into water) is recorded in Table IX.

An initial rapid drop over the first 6 hr. (total 16.5%) was followed by a much slower decomposition, which was not followed to infinity. If infinity is assumed to be zero, a plot of log $(A_\infty - A_t)$ *vs.* t gives a straight line, starting at 615 min. The slope is -4.1×10^{-7} sec.$^{-1}$. The decomposition rate for this portion of the curve is then 9.4×10^{-7} sec.$^{-1}$, and the half-life is approximately 9 days. The half-life of the initial change, on the other hand, is approximately 1 hr., which is of the same order of magnitude as the rate of cyclization of Ia. The extent of this initial change, when compared with expt. 10, Table I, suggests an equilibrium. That this was the case was indicated by product identification.

A 0.500-g. sample of IIa·HCl was heated under reflux with 1 l. of 3 *N* hydrochloric acid for 4.5 hr. After cooling, the solution was made alkaline with sodium hydroxide, which precipitated a cream-colored solid; 0.340 g. The ultraviolet spectrum was identical with that of IIa. The recovery was then 80%. The spectrum of the filtrate was identical with that of Ia in acid

Table VIII. Kinetics of Cyclization of Ia to IIa in 0.60 *N* Hydrochloric Acid at 94.1 ± 0.1°

Time, min.	A_t (385 mμ)	$A_\infty - A_t$	2 + log $(A_\infty - A_t)$
10	0.043	0.498	1.697
20	0.091	0.450	1.653
30	0.126	0.415	1.618
45	0.182	0.359	1.555
60	0.227	0.314	1.497
90	0.307	0.234	1.369
120	0.363	0.178	1.250
150	0.411	0.130	1.114
180	0.441	0.100	1.000
240	0.484	0.057	0.756
360	0.528	0.013	0.114
1157	0.541		
1360	0.541		

Table IX

Time, min.	O.D., 385 mμ	Time, min.	O.D., 385 mμ	Time, min.	O.D., 385 mμ
0	0.552	1410	0.451	6191	0.339
60	0.528	2025	0.431	7880	0.309
150	0.503	3263	0.402	9249	0.286
330	0.481	4695	0.371	12906	0.235
615	0.471				

(18) A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., 1961, p. 186.

and alkali, and indicated the presence of 0.0880 g. (19%).

Rate Measurements on Cyclization of Ib and Solvolysis of IIb. Solvent systems which were used included aqueous hydrochloric acid (1–6 *M*), aqueous sulfuric acid (0.06–8.8 *M*), and various alcohol or acetic acid–water–mineral acid mixtures (see Table IV).

For the experiments in aqueous sulfuric acid, concentrations of arylthiopyrimidine varied between 2.125×10^{-3} and 4.25×10^{-3} *M*. The higher molarities were used in the more dilute acid solutions, where less cyclization occurred; Ib was readily soluble in hydrochloric acid solutions, but could not be induced to dissolve in most of the sulfuric acid solutions at room temperature without the aid of a little ethanol (normally 1 ml./50 ml. of solution). The molarities of the more dilute sulfuric acid solutions were determined titrimetrically with standard sodium hydroxide and phenolphthalein indicator. The concentrations of solutions 2 *M* and above were determined from the densities (20°). The pyrimidine solutions were diluted 1:10 into water or 0.3 *M* sulfuric acid for spectral readings, which were recorded between 350 and 420 mμ.

The concentration of pyrimidobenzothiazine IIb used for measurement of rates of hydrolysis was 2.30×10^{-3} *M*. This compound presented a difficult solubility problem. Prolonged heating was required to dissolve it in most aqueous or alcoholic mineral acid solutions (usually 15 to 30 min. on the steam bath, accompanied by continuous pulverizing with a stirring rod), which caused some solvolysis. However, the substance was soluble in concentrated sulfuric acid at room temperature, with negligible decomposition during at least a 6-hr. period. The standard ultraviolet absorption curve was prepared by dissolving 0.0175 g. of IIb to make 5.00 ml. in concentrated sulfuric acid. Aliquots (0.1, 0.2, 0.3, and 0.4 ml.) were then diluted into 0.30 *M* sulfuric acid solutions and made up to final volumes of 50 ml. Spectra determined between 320 and 420 mμ showed that the substance obeyed Beer's law. The absorption maximum at 415 mμ (ε 8480) was used for determining A_t values.

Typical rate data obtained by carrying out the reaction in either direction (*i.e.*, starting with Ib or IIb, other conditions being equal) are found in Table X. These are the data of expt. 3, Table II, and expt. 1, Table III.

In a few instances the infinity absorbances decreased slightly with time (*ca.* 1%/day over several days). The optical densities were corrected for this change, which did not affect the linearity of the plots. This decomposition was only observed in a few instances. It was particularly high in one experiment (not reported here) in which Pyrex, rather than flint glass, ampoules were used, which suggests that borosilicates in the glass might be affecting the product.

For rate measurements carried out in alcoholic solvents, arylthiopyrimidine concentrations of 1.15×10^{-3} to 2.13×10^{-3} *M* were used. Solutions were diluted 1:10 into 0.1 *N* hydrochloric acid (aqueous) for spectral determinations. Water content in the solvents was either determined by the Karl Fischer method, or else known amounts of water were added to anhydrous solvents. Acid concentrations were determined titrimetrically. The acid strengths were found to decrease to varying degrees during the heating period in the ampoules, owing to some reaction with the solvent. (For example, a 0.290 *M* sulfuric acid solution in ethanol (13% water) had an acid strength of 0.208 *M* at the end of the kinetic run). The rate constants in alcoholic media cannot then be considered to be very accurate, but the uncertainty is not sufficient to affect the conclusions drawn in this paper.

Table X. Kinetics of Cyclization of Ib to IIb, and Hydrolysis of IIb to Ib (Typical Runs)

Cyclization of Ib[a] (2.04 *M* H_2SO_4)				Hydrolysis of IIb (2.06 *M* H_2SO_4)			
Time, min.	A_t (415 mμ)	$A_\infty - A_t$	$2 + \log (A_\infty - A_t)$	Time, min.	A_t (415 mμ)	$A_\infty - A_t$	$2 + \log (A_\infty - A_t)$
10	0.013	0.381	1.581	0[b]	0.820[b]	...	...
30	0.043	0.351	1.545	10	0.818	0.607	1.783
60	0.082	0.312	1.494	30	0.767	0.556	1.745
100	0.127	0.267	1.427	60	0.701	0.490	1.690
160	0.184	0.210	1.322	105	0.622	0.411	1.614
285	0.266	0.128	1.107	150	0.553	0.342	1.534
419	0.324	0.070	0.845	215	0.479	0.268	1.428
655	0.366	0.028	0.447	270	0.432	0.221	1.344
1315	0.393			480	0.297	0.086	0.935
1970	0.394			540	0.281	0.070	0.845
				1300	0.216		
				1700	0.211		
				1700	0.210		

[a] Initial concentration: 4.25×10^{-3} *M*. [b] Optical density after heating to dissolve compound; theoretical zero value is 0.920. Extent of reaction is calculated from latter value.

In alcoholic acid solutions of a concentration such that the product of the reaction, IIb, was not essentially all protonated, the substance reacted further to yield a new product which did not absorb in the 400–420-mμ region of the spectrum. Typical absorbance changes in such an experiment are shown in Table XI.

Table XI. Change in Optical Density (415 mμ) with Time in Reaction of Ib with 0.29 *M* Sulfuric Acid in Ethanol (13% Water)

Time, min.	O.D., 415 mμ	Time, min.	O.D., 415 mμ
10	0.027	360	0.344
30	0.077	360 (dupl.)	0.341
45	0.117	600	0.326
90	0.151	660	0.341
120	0.208	1129	0.216
180	0.246	1360	0.183
240	0.374	4495	0.016

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