5-Arylthiopyrimidines. III. Cyclization of 4-Hydroxy Derivatives to 10*H*-Pyrimido[5,4-*b*][1,4]benzothiazines (1,3-Diazaphenothiazines)[1]

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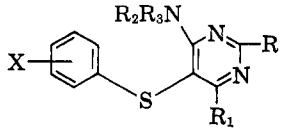
Received April 17, 1963

4-Hydroxy-5-bromopyrimidines containing a variety of electron-releasing substituents in the 2- and 6-positions react readily with *o*-aminothiophenoxide ion to produce 4-hydroxy-5-(*o*-aminoarylthio)pyrimidines. The products cyclize with ease by warming in dilute aqueous or alcoholic acid, to produce 10*H*-pyrimido[5,4-*b*][1,4]-benzothiazines. The parent compound of this new ring system was prepared from the 2-hydroxy derivative by chlorodehydroxylation, followed by hydrazinolysis and treatment with cupric ion. Other chemical transformations are described, as well as ultraviolet spectral characteristics and pK_a values of some of the products.

The preparation of a series of 4-substituted amino-5-arylthiopyrimidines (**1**) which had high pharmacological activity as hypotensive agents and serotonin antagonists[2] was recently reported by Roth and Hitchings.[3] It was observed that these structures bore a formal resemblance to the phenothiazines. It seemed probable that with appropriate ortho substituents in the benzene and pyrimidine rings of type **1** derivatives, cyclization could be effected to yield 1,3-diaza derivatives of the phenothiazines (10*H*-pyrimido[5,4-*b*]-[1,4]benzothiazines) (**2**). Such products would be of



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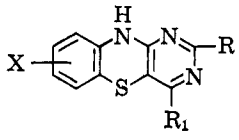

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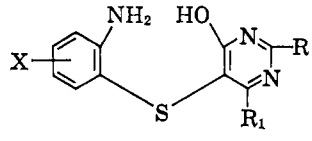
biological interest because of their relationship to the isoalloxazines, such as riboflavin, to the pharmacologically active phenothiazines such as chlorpromazine, and to the previously mentioned hypotensive 5-arylthiopyrimidines.

This paper presents further information on the reactivity of 5-halopyrimidines with thiophenoxide ion, describes a facile ring closure to produce 10*H*-pyrimido-[5,4-*b*][1,4]benzothiazines, which does not seem to have been utilized previously in related systems, and records some physical and chemical properties of this ring system.

A number of mono- and diaza derivatives of the phenothiazines have been reported in recent years. Most of these are pyridobenzothiazines or dipyridothiazines.[4] Prior to the initiation of this investigation, the only reported diazaphenothiazines with both nitrogens in the same ring were 10*H*-pyridazino[4,3-*b*][1,4]-benzothiazines.[5,6]

When the present investigation was essentially complete, a patent[7] appeared describing 1,3- and 2,4-diazaphenothiazines with hydrogen, alkyl, or aryl groups in the 2,4- or 1,3-positions, respectively. These were prepared from 4,5-dihalopyrimidines, by reaction of the 4-halo group with *o*-aminothiophenol.[8] This method was utilized by Phillips and co-workers[9] of these laboratories to prepare 2,4-diamino-10*H*-pyrimido[5,4-*b*][1,4]benzothiazine.

It was our aim to investigate the preparation of this ring system from 4-hydroxy-5-(*o*-aminoarylthio)pyrimidines (**3**), either by direct cyclization or by ring



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closure following conversion of the 4-hydroxyl substituent to a better leaving group, such as 4-halo. The first objective, then, was the synthesis of type **3** derivatives.

Results and Discussion

Synthesis of 5-Arylthio-4-hydroxypyrimidines.—*o*-Aminothiophenoxide ion was found to condense with 5-bromoisocytosine and 5-bromouracil in a manner similar to that described in part II of this series,[3] in ethylene glycol solvent at 120–130°, with potassium carbonate as the base. The products were the desired 5-(*o*-aminophenylthio)pyrimidines of type **3**.

Up to this time, only 5-bromoisocytosine and 5-bromouracils were known to produce 5-arylthiopyrimidines with thiophenols. Attention was then turned

(1) Presented in part at the 140th National Meeting of the American Chemical Society, Chicago, Ill., September, 1961.

(2) (a) C. H. Ellis, *Am. J. Physiol.*, **199**, 167 (1960); (b) K. I. Colville, M. M. Jacobson, and C. H. Ellis, *Federation Proc.*, **19**, 120 (1960); (c) K. I. Colville and L. A. Lindsay, *ibid.*, **21**, 174 (1962).

(3) B. Roth and G. H. Hitchings, *J. Org. Chem.*, **26**, 2770 (1961) (part II of this series).

(4) (a) V. A. Petrow and E. L. Rewald, *J. Chem. Soc.*, 591 (1945); (b) T. Takahashi and E. Yoshii, *Pharm. Bull.* (Japan), **2**, 382 (1954); *Chem. Abstr.*, **50**, 13032 (1956); (c) Y. Maki, *Yakugaku Zasshi*, **77**, 485 (1957); *Chem. Abstr.*, **51**, 14738 (1957); (d) Y. Maki, *Yakugaku Zasshi*, **77**, 862 (1957); *Chem. Abstr.*, **52**, 1174 (1958); (e) T. Takahashi and Y. Maki, *Yakugaku Zasshi*, **78**, 417 (1958); *Chem. Abstr.*, **52**, 14622 (1958); (f) T. Takahashi and Y. Maki, *Chem. Pharm. Bull.* (Tokyo), **6**, 369 (1958); *Chem. Abstr.*, **53**, 9228 (1959); (g) H. L. Yale and F. Sowinski, *J. Am. Chem. Soc.*, **80**, 1651 (1958); (h) A. J. Saggiomo, P. N. Craig, and M. Gordon, *J. Org. Chem.*, **23**, 1906 (1958); (i) A. R. Gennaro, *ibid.*, **24**, 1156 (1959); (*j*) F. H. Clarke, G. B. Silverman, C. M. Watnick, and N. Sperber, *ibid.*, **26**, 1126 (1961); (k) E. Kopp and M. Strell, *Arch. Pharm.*, **295**, 99 (1962); (l) W. A. Schuler and H. Klebe, *Ann.*, **653**, 172 (1962); (m) French Patent 1,170,119; *Chem. Abstr.*, **55**, 9437 (1961).

(5) J. Druey, *Angew. Chem.*, **70**, 5 (1958).

(6) Their preparation is illustrated by the condensation of 3,4,6-trichloropyridazine with *o*-aminothiophenol in the presence of base, to form 3,6-dichloro-4-(*o*-aminophenylthio)pyridazine, which then was cyclized by acid. Methods used for the preparation of the pyridine systems mentioned previously included that used for the pyridazines, as well as Smiles type rearrangements of *o*-nitro-(*o'*-acylaminophenylthio)pyridines, fusion of N-pyridylanilines with sulfur, and condensation of *o*-nitrochloropyridines or *o*-nitromethoxybenzenes with *o*-aminothiophenols or the corresponding pyridine derivatives.

(7) A. Westermann, O. Bub, and L. Suranyi, German Patent 1,110,651 (July, 1961); *Chem. Abstr.*, **56**, 2461 (1962).

(8) The products were either 4-anilino- or 4-arylthiopyrimidines, depending on whether acidic or alkaline media were employed for the nucleophilic substitution. These intermediates cyclized in boiling dimethylformamide to yield identical pyrimido[5,4-*b*][1,4]benzothiazines. Evidently a Smiles rearrangement occurred in the instance of the 4-arylthiopyrimidines.

(9) A. P. Phillips, N. B. Mehta, and J. Z. Strelitz, *J. Org. Chem.*, **28**, 1488 (1963).

to other variations in the pyrimidine nucleus. A series of 2-mono- and dialkylamino-4-hydroxypyrimidines was prepared. These were found to be brominated readily in the 5-position. It might be supposed that with the strongly electron releasing dialkylamino groups in the 2-position, reactivity of the 5-bromo group to nucleophilic substitution would be decreased. However, all of these compounds reacted readily with thiophenoxide ion in warm dilute ethanol, and did not produce undue amounts of 5-unsubstituted pyrimidine. This does not constitute proof that these derivatives were more reactive than 5-bromoisocytosine, however. Their greater solubility in alcoholic solvents may provide the explanation. Nevertheless, it is of considerable interest that 5-halopyrimidines of this type can be substituted with ease.

Introduction of a methyl substituent into the 6-position of the 5-bromo-2-dialkylamino-4-hydroxypyrimidines had no apparent adverse effect on the reaction with thiophenoxide derivatives. However, a 6-hydroxyl substituent facilitated the reaction. The 6-hydroxyl analog of 5-bromoisocytosine produced nearly quantitative yields of 5-arylthio derivative using dilute ethanol as the solvent. This was the first instance where there was no tendency for reductive removal of the 5-bromo group.[3]

5-Bromo-2-thiouracil produced a 5-arylthio derivative with *o*-aminothiophenol; the yield was very poor, however. The corresponding 2-methylthiopyrimidine was attacked in the 2-position by *o*-aminothiophenoxide ion. A mixture of produc s was obtained and the reaction was found to be unsatisfactory for preparing a 5-arylthio derivative.

Variations also were made in the benzene ring substituents of the *o*-aminothiophenols. Besides *o*-aminothiophenol, its 4-chloro and 4,5-dimethyl derivatives were employed in reactions with 5-halopyrimidines. Although 5-arylthiopyrimidines were produced with approximate equal facility with the two former derivatives, the last named thiophenol oxidized very rapidly and gave poor yields of arylthio derivatives which were difficult to purify.

Cyclization of 5-(*o*-Aminoarylthio)-4-hydroxypyrimidines to 10*H*-Pyrimido[5,4-*b*][1,4]benzothiazines. (A) Methods.—The readily prepared 2-amino-4-hydroxy-5-(*o*-aminophenylthio)pyrimidine was used as a model in a study of cyclization methods. Attempts to cyclize this intermediate directly under strongly dehydrating conditions failed. No cyclization occurred in concentrated sulfuric acid at temperatures up to 200°. Phosphoryl chloride was then tried, with the hope of obtaining either cyclization or replacement of the 4-hydroxyl substituent by 4-chloro, which would be expected to be a good leaving group under acid conditions.[10] It appeared that cyclization occurred directly, but produced a phosphorylated derivative from which it was difficult to isolate the desired product in acceptable yield. Protection of the amino groups by acetylation, prior to reaction with phosphoryl chloride, was investigated. This did afford the desired 2-amino-10*H*-pyrimido[5,4-*b*][1,4]benzothiazine, after acid hydrolysis to remove acetyl groups. However, the intermediate acetylated derivative was of doubtful composition, and, therefore, it was treated with 2 *N* hydrochloric acid to determine whether the 2-amino-4-hydroxy-5-(*o*-aminophenylthio)pyrimidine could be recovered. Some starting material was indeed found; however, there was also formed a bright yellow product, which proved to be the desired pyrimidobenzothiazine.

The starting material was then treated with 2 *N* hydrochloric acid under similar conditions, and approximately the same amount of cyclized derivative was obtained. Conditions were varied, and it was found that when 2-amino-4-hydroxy-5-(*o*-aminophenylthio)pyrimidine was heated with 1 *N* hydrochloric acid in 85% ethanol for six hours, an 80% yield of excellent quality 2-amino-10*H*-pyrimido[5,4-*b*][1,4]benzothiazine hydrochloride was obtained. This appeared to be the method of choice for producing the pyrimidobenzothiazines. A search for optimum conditions indicated that maximum yields were obtained at acid concentrations between 0.2–1 *N*. Sulfuric and hydrochloric acids seemed equally satisfactory, but weak acids, such as acetic acid, were ineffective.

To determine the scope of this reaction, the corresponding 2,4-dihydroxy-5-(*o*-aminophenylthio)pyrimidine was next investigated. It was found that cyclization proceeded in ethanolic, but not aqueous, medium. Longer heating (twenty-four hours) was required than with the 2-amino derivative, possibly due to the relative insolubility of the hydrochloride of the starting material.

All of the remaining 5-arylthiopyrimidines which had been synthesized were treated with 0.2–1.2 *N* hydrochloric acid in 80–90% ethanol (conditions were varied a bit depending on solubility characteristics), and in every instance the pyrimidine cyclized readily. The course of the reaction could be observed by the development of a yellow color in the solutions. Table V lists the individual results. In a number of instances it was not possible to ascertain yields, because the arylthiopyrimidines were used in a crude state, contaminated with 5-halo or 5-unsubstituted pyrimidines. These impurities were readily separated from the cyclized products, which were insoluble in alkali, in contrast with the 4-hydroxypyrimidine intermediates.

(B) Mechanism.—This acid-catalyzed cyclization, which we have found to be general for all 4-hydroxy-5-(*o*-aminoarylthio)pyrimidines tested, is considered to proceed *via* initial protonation of a pyrimidine ring nitrogen. This activates nucleophilic attack by a nonprotonated anilino nitrogen on the positive 4-carbon of the pyrimidine ring, which carries the hydroxy group. The resulting complex, tetrahedral at the site of substitution, eliminates water and forms the cyclization product.

A maximum reaction rate would be expected at that acidity where the product of concentrations of species with the pyrimidine ring monoprotonated and with the anilino group unprotonated would be maximum. When all centers were protonated, no reaction would be expected. This is indeed the case. No reaction occurs in concentrated acid. The kinetics of these reactions have been studied by one of us (B.R.) over a range of acid concentrations and solvents, and will be reported in a future communication.

Banks[10] used similar terms to explain the activation of α- and γ-halosubstituted nitrogen heterocycles to nucleophilic substitution by anilines in acid medium.

(10) C. K. Banks, *J. Am. Chem. Soc.*, **66**, 1127 (1944).

The effect also has been discussed by Lythgoe.[11] However, there has been no demonstration in pyrimidine chemistry that a hydroxyl substituent can become a leaving group by such a mechanism. There are a few instances on record of nucleophilic displacement of hydroxyl groups in aromatic compounds. A German patent[12] describes the replacement of the 4-hydroxyl group of 2,4-dihydroxyquinoline by amines. This was further investigated by Curd, *et al.*,[13] who confirmed that displacement occurred exclusively in the 4-position with aliphatic amines at 150–250°. There was no reaction with aniline, but in the presence of hydrochloric or boric acids, 90% yields of the 4-anilino derivatives were obtained at 180–190° (forty hours). Phenoxazines have been prepared by the pyrolysis of aminophenols, plus catechol derivatives at 200°.[14] Aminolysis of the phenolic substituent of 3-nitro-4-hydroxybenzenearsonic acid by 2-aminoethanol was reported by Sweet, *et al.*[15] Bunnett, *et al.*,[16] found that 4-phenylazo-1-naphthol is etherified by methanol and ethanol in acid medium, due to nucleophilic displacement on the aromatic carbon. The protonated azo linkage is the activating group, and is shown to have features in common with the protonated hetero nitrogen. Bunnett and Zahler[17] have discussed a number of other reactions which result in replacement of hydroxyl groups by other substituents, such as reaction with phosphoryl chloride, to produce chloro derivatives, but state that these, no doubt, proceed *via* other intermediates.

Chemical Transformations with 10*H*-Pyrimido[5,4-*b*][1,4]benzothiazines.—With the 10*H*-pyrimido[5,4-*b*][1,4]benzothiazine skeleton at hand, it was of interest to determine what transformations of substituents could be accomplished. The 2-hydroxy- and 2-hydroxy-8-chloro derivatives were investigated first. Chlorodehydroxylation with phosphoryl chloride was found to yield the 2-chloro derivatives, along with intractable by-products.

The 2-chloro-10*H*-pyrimido[5,4-*b*][1,4]benzothiazines reacted readily with a variety of nucleophilic reagents. N-Methylpiperazine and 3-dimethylaminopropylamine produced derivatives identical with those prepared by complete synthesis from the 2-alkylaminopyrimidines (**2**, R = $-N(CH_2CH_2)_2NCH_3$, $-NHCH_2CH_2OH_2N(CH_3)_2$; R_1 = H; X = H). Thus, we were indeed working with the same ring system *via* both routes.

Other nucleophilic reagents which were used successfully included other amines, hydrazine, methoxy and methoxyethoxy ions, and thiourea, which produced the 2-mercapto derivative. The latter was identical with the substance produced by direct synthesis.

Various attempts were made to remove the halogen from 2-chloro-10*H*-pyrimido[5,4-*b*][1,4]benzothiazine by reductive means. Initial reactions with zinc were unsuccessful, as was an attempt to use *p*-toluenesulfonhydrazide (see Experimental section). However, with hydrazine the 2-hydrazino derivative was formed readily and almost quantitatively. When this was dissolved in hot dilute acid, it reacted with cupric ion to give an immediate precipitate, which gradually evolved nitrogen and produced the parent member of this ring system. An attempt was made to prepare 8-chloro-10*H*-pyrimido[5,4-*b*][1,4]benzothiazine from the 2-hydrazino-8-chloro derivative by similar means. However, the latter compound is so exceedingly insoluble in aqueous acids that this approach was unsuccessful. Reduction by zinc was finally accomplished, however, in hot 2-methoxyethanol containing a little acetic acid and water.

Ultraviolet Absorption Spectra.—The ultraviolet absorption spectra of the intermediate pyrimidines are described in Table VI, and those of the pyrimidobenzothiazines in Table VII. The 2-dialkylamino-4-hydroxypyrimidines all have similar spectra. The spectra of the cationic species exhibit a large hypsochromic displacement, and the anionic species a lesser displacement, from those of the neutral molecules. This is to be expected as a consequence of resonance of the electron-releasing 2-dialkylamino substituent, which will be diminished to the greatest extent on protonation. 5-Halogenation confers an expected bathochromic shift, to the extent of 14 to 18 mμ in the longer wavelength peak, and 5–10 mμ in the shorter wave-length maximum. Methylation in the 6-position brings the peaks closer together; *i.e.*, there is a slight bathochromic shift of the lower wave length maximum, and a slight hypsochromic shift of the higher wave-length peak.

All of the 2-alkylamino-4-hydroxy-5-(*o*-aminoarylthio)pyrimidines have spectra which are very much alike, so only a few are listed in Table VI for illustrative purposes. The spectra of the 5-arylthio derivatives are also very much like their 5-bromo precursors. In acid solution, the maxima of the arylthio derivatives are reduced to shoulders, but at about the same wave lengths as the bromopyrimidine maxima. In alkali the maxima for the arylthio derivatives are shifted to slightly longer wave lengths as compared to the 5-bromopyrimidines, particularly in the lower wavelength peak; they also have about 25% higher extinction values. The highest molecular extinction values that were obtained with the 5-arylthio derivatives were in the vicinity of 20,000–25,000.

The ultraviolet absorption spectra of 10*H*-pyrimido-[5,4-*b*][1,4]benzothiazine and its 2-amino derivative are shown in Fig. 1 and 2. These depict the neutral molecules, the monoprotonated species, and the spectrum at an intermediate pH value, so that isosbestic points can more readily be seen. These spectra differ markedly from those of the 4-hydroxy-5-arylthiopyrimidines, but bear a closer resemblance to those of the corresponding 4-amino derivatives.[3] However, they are distinguished by very markedly higher extinction values in the 240–250-mμ region of the spectrum and by absorption with low peaks out to the 400-mμ region.

The neutral species of 10*H*-pyrimido[5,4-*b*][1,4]-benzothiazine is distinguished by an intense maximum at 249 mμ and a minor peak at 340 mμ. Monoprotonation creates a bathochromic shift of 12 mμ in the major

(11) B. Lythgoe, *Quart. Rev.*, **3**, 198 (1949).

(12) K. Arnim, to I. G. Farbenindustrie A.-G., German Patent 681,980; *Chem. Abstr.*, **36**, 2273 (1942).

(13) F. H. S. Curd, C. G. Raison, and F. L. Rose, *J. Chem. Soc.*, 899 (1947).

(14) D. E. Pearson in "Heterocyclic Compounds," Vol. 6, R. C. Elderfield, Ed., John Wiley and Sons, Inc., New York, N. Y., 1957, p. 685.

(15) L. A. Sweet, D. G. Calkins, and C. K. Banks, *J. Am. Chem. Soc.*, **69**, 2260 (1947).

(16) J. F. Bunnett, E. Buncel, and K. V. Nahabedian, *ibid.*, **84**, 4136 (1962).

(17) J. F. Bunnett and R. E. Zahler, *Chem. Rev.*, **49**, 273 (1951).

TABLE I

pK_a VALUES OF 10*H*-PYRIMIDO[5,4-*b*][1,4]BENZOTHIAZINES

Compound	Substituent	pK_a[a]
LVI	...	3.76
LVII	8-Cl	3.43
LIV	2-CH_3O	3.45
XXIX	2-NH_2	5.61

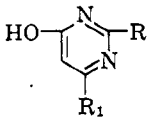
[a] Accurate to ±0.05 pH units.

indicative of the structures of these products, as all belonging to the same ring system.

pK_a Values.—The pK_a values of the parent 10*H*-pyrimido[5,4-*b*][1,4]benzothiazine and some simple derivatives are listed in Table I. These values were determined spectrophotometrically. Isosbestic points were established in all cases as a criterion of the number of equilibria involved.

TABLE II

2-ALKYLAMINO-4-HYDROXYPYRIMIDINES

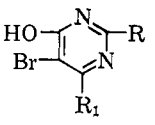


Compound	R	R_1	M.p., °C.	Recrystallization solvent[a]	Empirical formula	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
I	$-(CH_2)_5N-$	H	156–157	A	$C_9H_{13}N_3O$	60.31	7.74	23.44	60.39	7.15	23.44
II	$-CH_2CH_2OCH_2CH_2-N-$	H	169–170	B	$C_8H_{11}N_3O_2$	53.02	6.12	23.19	53.24	5.77	22.76
III	$-CH_2CH_2OCH_2CH_2-N-$	CH_3	239–243	A	$C_9H_{13}N_3O_2$	55.37	6.71	21.53	55.08	6.35	21.41
IV	$CH_3N(CH_2CH_2)_2N-$	H	185–186	C, A	$C_9H_{14}N_4O$	55.65	7.27	28.85	55.74	7.02	28.56
V	$CH_3N(CH_2CH_2)_2N-$	CH_3	154–155	A	$C_{10}H_{16}N_4O$	57.67	7.74	26.90	57.92	7.69	26.85
VI[b]	$(CH_3)_2NCH_2CH_2CH_2NH-$	H	(syrup)								

[a] A, ethyl acetate; B, 95% ethanol; C, absolute ethanol. [b] Purified as 5-bromo derivative.

TABLE III

5-BROMO-4-HYDROXYPYRIMIDINES



Compound	R	R_1	M.p., °C.	Recrystallization solvent[a]	Empirical formula	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
VII[b]	$(CH_3)_2N-$	CH_3	232–233	A	$C_7H_{10}BrN_3O$	36.22	4.34	18.11	36.28	4.45	18.17
VIII	$-(CH_2)_5N-$	H	201–202	B	$C_9H_{12}BrN_3O$	41.87	4.68	16.28	42.28	4.44	16.16
IX[c]	$-(CH_2)_5N-$	CH_3	242–243	B	$C_{10}H_{14}BrN_3O$	44.13	5.18	15.44	44.37	4.87	15.22
X	$-CH_2CH_2OCH_2CH_2N-$	H	238–241	B	$C_8H_{10}BrN_3O_2$	36.94	3.87	16.15	37.09	3.55	15.80
XI	$-CH_2CH_2OCH_2CH_2N-$	CH_3	240–243	B	$C_9H_{12}BrN_3O_2$	39.43	4.44	15.33	39.82	4.98	15.16
XII	$CH_3N(CH_2CH_2)_2N-$	H	280–282 dec.	C	$C_9H_{13}BrN_4O\cdot HBr$	30.53	3.99	15.83	30.91	4.11	15.49
XIII	$CH_3N(CH_2CH_2)_2N-$	CH_3	274–275 dec.	D	$C_{10}H_{15}BrN_4O\cdot HBr\cdot 0.5H_2O$	31.85	4.54	14.86	31.71	4.56	14.60
XIV	$(CH_3)_2NCH_2CH_2CH_2NH-$	H	128–129	B	$C_9H_{15}BrN_4O\cdot HBr\cdot H_2O$	28.89	4.85	14.98	29.05	4.40	14.53

[a] A, reprecipitated from alkali; B, 95% ethanol; C, ethanol–water; D, water. [b] From 2-dimethylamino-4-hydroxy-6-methylpyrimidine by method of C. G. Overberger and I. C. Kogon, *J. Am. Chem. Soc.*, **76**, 1879 (1954); see also P. B. Russell, G. B. Elion, and G. H. Hitchings, *ibid.*, **71**, 474 (1949); our product had m.p. 181° (from EtOH). [c] From 4-hydroxy-6-methyl-2-piperidinopyrimidine (ref. 20c).

peak, and introduces two minor peaks at 315 and 360 mμ, indicating increased resonance of the cation.

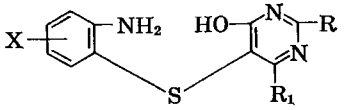
The 2-amino derivative has an intense peak at 240 mμ, which undergoes a hyperchromic shift on protonation, accompanied by formation of a new peak and three shoulders in the 260–300-mμ region, as well as a bathochromic shift in the minor peak to 385 mμ. These results indicate protonation on a pyrimidine ring nitrogen, rather than on the 2-amino or 10-nitrogen. The former would be expected to increase the resonance, whereas the latter would be expected to decrease it, since the capacity of the amino groups to contribute electrons would be lessened. The spectra of all the other pyrimidobenzothiazines of Table VII bear similar properties. These data may be considered as strongly

The unsubstituted pyrimidobenzothiazine is a weak base. It is made weaker, as expected, by introduction of an 8-chloro substituent, and also by a 2-methoxy substituent. The 2-amino derivative is also rather weakly basic. The pK_a value of 5*H*-pyrido[3,4-*b*]-[1,4]benzothiazine (3-azaphenothiazine) has been reported by Clarke, *et al.*,[4j] as 5.88. This increased basicity is not at all surprising, since pyridine is a much stronger base (pK_a 5.2) than pyrimidine (pK_a 1.31). The pyrimidobenzothiazine pK_a values may be compared with those of the aminopyrimidines.[18] 2- and 4-Aminopyrimidines have pK_a values of 3.54 and 5.71, respectively, and 2,4-diaminopyrimidine has a pK_a

(18) D. J. Brown, "The Pyrimidines," John Wiley and Sons, Inc., New York, N. Y., 1962, pp. 468–470.

TABLE IV

5-(*o*-AMINOARYLTHIO)-4-HYDROXYPYRIMIDINES

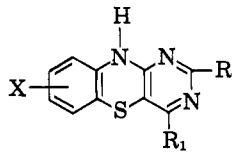


Compound	R	R_1	X	Reaction medium[a] (temp., °C.)	Reaction time, hr.	Yield,[b] %	Recrystallization solvent[c]	M.p., °C.	Empirical formula	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
XV	OH	H	...	A (120–130)	1	40	D	247–249 dec.	$C_{10}H_9N_3O_2S$	51.07	3.86	17.87	51.40	4.02	17.70
				A (120–145)	4	20									
				A (150)	2	21									
XVI	OH	H	4-Cl	A (120)	1	30	D	297–300 dec.	$C_{10}H_8ClN_3O_2S$	44.53	2.99	15.58	44.41	3.01	15.26
XVII	NH_2	H	...	A (140–150)	3	56	D	265–267	$C_{10}H_{10}N_4OS$	51.26	4.30	23.92	51.13	4.50	23.58
XVIII	NH_2	H	4-Cl	A (140–150)	3	56	E	255–258 dec.	$C_{10}H_9ClN_4OS$	44.70	3.38	20.85	44.69	3.61	21.00
XIX	NH_2	OH	...	C	3	93	..	310–320 dec.	$C_{10}H_{10}N_4O_2S \cdot H_2O$	44.77	4.51	20.88	45.05	4.23	20.62
XX	$(CH_3)_2N$—	CH_3	...	A (140)	2	60	F	216	$C_{13}H_{16}N_4OS$	56.49	5.84	20.27	56.78	5.97	20.88
XXI	$(CH_2)_5N$—	H	4-Cl	B	3.5	60	F	226–228	$C_{15}H_{17}ClN_4OS$	53.48	5.09	16.63	53.64	5.01	16.85
XXII	$(CH_2)_5N$—	CH_3	4-Cl	B	3	40	F	218–220	$C_{16}H_{19}ClN_4OS$	54.77	5.46	15.97	54.52	4.99	15.47
XXIII	$CH_2CH_2OCH_2CH_2N$—	H	4-Cl	B	4	62	F	237–239	$C_{14}H_{15}ClN_4O_2S$	49.63	4.46	16.54	49.43	4.54	16.10
XXIV	$CH_2CH_2OCH_2CH_2N$—	CH_3	4-Cl	B	2.5	41	F	225–228	$C_{15}H_{17}ClN_4O_2S$	51.06	4.86	15.88	50.94	4.80	15.64
XXV	$CH_3N(CH_2CH_2)_2N$—	H	4-Cl	C	2.5	41	F	226–228	$C_{15}H_{18}ClN_5OS$	52.01	5.16	19.91	51.65	4.60	19.65
XXVI	$CH_3N(CH_2CH_2)_2N$—	CH_3	4-Cl	B	3	50	F	229–232	$C_{16}H_{20}ClN_5OS$	52.52	5.51	19.14	52.54	5.14	18.97

[a] A, ethylene glycol plus K_2CO_3; B, 65% ethanol plus K_2CO_3 at boil; C, 50% ethanol plus K_2CO_3 at boil. [b] Average yields are recorded, in cases of more than one run; yields are of semipure products, after extraction of impurities prior to recrystallization. [c] Products were in all cases reprecipitated from solution in dilute sodium hydroxide to remove residual diaryl disulfide prior to recrystallization: D, 2-methoxyethanol; E, 80% ethanol; F, 95% ethanol.

TABLE V

10*H*-PYRIMIDO[5,4-*b*][1,4]BENZOTHIAZINES *via* CYCLIZATION OF 5-(*o*-AMINOARYLTHIO)-4-HYDROXYPYRIMIDINES



Compound	R	R_1	X	Reaction medium	Reaction time, hr.	Yield, %	Recrystallization solvent
XXVII	OH	H	...	87% EtOH, 1 *N* HCl	16	75	1 *N* HCl in EtOH, NaOH
XXVIII	OH	H	8-Cl	87% EtOH, 1 *N* HCl	18	41	Extd. NaOH
XXIX	NH_2	H	...	87% EtOH, 1 *N* HCl	6	80	0.2 *N* HCl in 85% EtOH EtOH–H_2O
XXX	NH_2	H	8-Cl	90% EtOH, 0.6 *N* HCl	18	90	2-Methoxyethanol
XXXI	NH_2	H	7,8-$(CH_3)_2$	70% EtOH, 0.7 *N* HCl	6.5	61[a]	EtOH–H_2O
XXXII	NH_2	OH	...	90% EtOH, 0.6 *N* HCl	24	20	EtOH–HCl
XXXIII	$(CH_3)_2N$—	CH_3	...	80% EtOH, 1 *N* HCl	6	88	EtOH
XXXIV	—$(CH_2)_5N$—	H	...	85% EtOH, 1.2 *N* HCl	15	..[c]	EtOH
XXXV	—$(CH_2)_5N$—	H	8-Cl	95% EtOH, 0.2 *N* HCl	15	43	EtOH
XXXVI	—$(CH_2)_5N$—	CH_3	8-Cl	90% EtOH, 0.4 *N* HCl	16	..	EtOH
XXXVII	—$CH_2CH_2OCH_2CH_2N$—	H	...	85% EtOH, 1.4 *N* HCl	15	37[d]	EtOH
XXXVIII	—$CH_2CH_2OCH_2CH_2N$—	H	8-Cl	90% EtOH, 0.25 *N* HCl	17	62	EtOH
XXXIX	—$CH_2CH_2OCH_2CH_2N$—	CH_3	8-Cl	85% EtOH, 1 *N* HCl	17	41	EtOH
XL	$CH_3N(CH_2CH_2)_2N$—	H	...	85% EtOH, 1 *N* HCl	5	..[c]	EtOH–HCl
XLI	$CH_3N(CH_2CH_2)_2N$—	CH_3	...	85% EtOH, 1 *N* HCl	4	..[c]	EtOH + 2 equiv. HCl
XLII	$CH_3N(CH_2CH_2)_2N$—	H	8-Cl	90% EtOH, 0.6 *N* HCl	17	56	EtOH
XLIII	$CH_3N(CH_2CH_2)_2N$—	CH_3	8-Cl	90% EtOH, 0.6 *N* HCl	20	70	EtOH–H_2O, hexane
XLIV	$(CH_3)_2N(CH_2)_3NH$—	H	...	80% EtOH, 0.6 *N* HCl	18	..[c]	EtOH–HCl

[a] From crude arylthio derivative. This was prepared from 5-bromoisocytosine and 2-amino-4,5-dimethylthiophenol, obtained as the hydrochloride salt from the Aldrich Chemical Co.; disulfide, m.p. 124–126° (from ethanol). *Anal.* Calcd. for $C_{16}H_{20}N_2S_2$: C,

of 7.3. The pyrimidobenzothiazine basicities are correspondingly weaker, as would be expected, due to the influence of the benzene ring.

Pharmacological Investigations.—The preparation of 10-substituted derivatives of this pyrimidobenzothiazine series has been accomplished, and will be reported at a future date, along with pharmacological data on the products. The physiological properties of the compounds reported here are under current investigation, and will be reported elsewhere.

Experimental[19]

2-Alkylamino-4-hydroxypyrimidines.—Several new 2-alkylamino-4-hydroxypyrimidines and 6-methyl analogs were synthesized by the reaction of 4-hydroxy-2-methylthiopyrimidine or its 6-methyl derivative with alkylamines and substituted alkylamines.[20] These products are characterized in Table II.

2-Alkylamino-5-bromo-4-hydroxypyrimidines.—These derivatives were prepared from the corresponding 5-unsubstituted pyrimidines by bromination in glacial acetic acid. The pyrimidines were dissolved in approximately 15 volumes of glacial acetic acid, and the bromine was added dropwise at room temperature. The product usually precipitated as the white hydrobromide salt; ether was added in other cases to effect precipitation. The products were usually converted to the free bases for purification; yields of purified products ranged between 55–80%. In a few instances, instability of the products was noted upon warming in dilute acid. The extinction value of compound IX, for example, decreased with time in 0.1 *N* hydrochloric acid. New 5-bromopyrimidines are characterized in Table III.

5-(*o*-Aminoarylthio)-4-hydroxypyrimidines.—The preparation of 5-(*o*-aminoarylthio)isocytosine and uracil derivatives was carried out according to the directions of Roth and Hitchings,[3] from the 5-halopyrimidine and *o*-aminothiophenol or its derivatives. It was found that yields could be improved somewhat in the case of the uracil derivatives by lowering the reaction temperature to 120–130°. This is the approximate temperature at which these pyrimidines dissolve in glycol medium. The 2-alkylamino-4-hydroxy-5-bromopyrimidines reacted with thiophenols with considerably greater facility than was the case with 5-bromoisocytosine; alcohol–water mixtures were used as the solvent, in the presence of potassium carbonate. In a few cases, the arylthio derivatives were obtained as gums which could not be readily crystallized. In these cases, it was usually found easier to proceed directly with the cyclization reaction (described later) to produce the pyrimidobenzothiazines. The intermediate arylthiopyrimidines were sometimes contaminated with unchanged 5-halopyrimidine, which had solubility properties similar to the arylthio derivatives; however, upon cyclization, the products were no longer soluble in alkali, whereas the 5-halopyrimidines (or 5-unsubstituted pyrimidines) were readily soluble, and thus could be readily separated from the product. Table IV summarizes the data on the 5-arylthiopyrimidines. An example is given in the following section.

5-(*o*-Amino-*p*-chlorophenylthio)-4-hydroxy-2-piperidinopyrimidine (XXI).—A mixture of 12.9 g. (0.05 mole) of 5-bromo-4-hydroxy-2-piperidinopyrimidine, 9.8 g. (0.05 mole) of *o*-amino-*p*-chlorothiophenol hydrochloride, 10.3 g. (0.075 mole) of potassium carbonate, 120 ml. of 95% ethanol, and 80 ml. of water was refluxed on the steam bath for 3.5 hr. The color of the mixture, which at all times contained insoluble material, gradually changed from yellow to nearly white. It was cooled, and the precipitate isolated. Concentration of the filtrate yielded an additional precipitate, which was added to the previous precipitate. The product was slurried in dilute sodium hydroxide, which dissolved

(19) All 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.

(20) (a) T. B. Johnson and K. G. Mackenzie, *Am. Chem. J.*, **42**, 353 (1909); (b) F. H. S. Curd, M. I. Davis, E. C. Owen, F. L. Rose, and G. A. P. Tuey, *J. Chem. Soc.*, 370 (1946); (c) R. Hull, B. J. Lovell, H. T. Openshaw, L. C. Payman, and A. R. Todd, *ibid.*, 357 (1946).

TABLE V (*continued*)

M.p., °C.	Empirical formula	Calcd. C	Calcd. H	Calcd. N	Calcd. Cl	Calcd. S	Found C	Found H	Found N	Found Cl	Found S
ca. 380	$C_{10}H_7N_3OS$	55.28	3.25	19.35	...	...	55.26	3.19	19.29	...	...
>360	$C_{10}H_6ClN_3OS$	47.72	2.40	16.70	...	...	47.64	2.30	16.71	...	...
236–238	$C_{10}H_8N_4S \cdot HCl$	47.52	3.59	22.17	12.69	14.03	47.44	3.84	22.19	12.71	14.38
235	$C_{10}H_8N_4S$	55.53	3.73	...	...	...	55.35	4.19	...	...	...
328–329	$C_{10}H_7ClN_4S$	47.91	2.81	22.31	...	...	47.70	2.97	22.06	...	...
303–309	$C_{12}H_{12}N_4S \cdot HCl$	51.33	4.67	19.95	12.63	...	51.11	4.62	20.49	12.36	...
300 dec.	$C_{10}H_8N_4OS \cdot HCl$	44.69	3.37	20.85	...	...	45.87	3.61	21.09	...	...
218–220 dec.	$C_{18}H_{14}N_4S \cdot HCl \cdot H_2O$[b]	49.91	5.48	17.91	11.33	...	49.77	5.33	17.96	11.5	...
142–144	$C_{15}H_{16}N_4S$	63.35	5.67	19.70	...	...	63.37	5.56	19.83	...	...
165–167	$C_{15}H_{15}ClN_4S$	56.51	4.74	17.57	11.13	...	56.82	4.73	17.21	11.49	...
211–212	$C_{16}H_{17}ClN_4S$	57.43	5.15	16.83	...	...	57.75	5.12	16.80	...	...
177–179	$C_{14}H_{14}N_4OS$	58.72	4.64	19.57	...	...	58.93	4.78	19.56	...	...
193	$C_{14}H_{13}ClN_4OS$	52.41	4.08	17.66	...	...	52.40	3.94	17.24	...	...
233–234	$C_{15}H_{15}ClN_4OS$	53.51	4.52	16.73	...	...	53.64	4.29	16.39	...	...
139	$C_{15}H_{17}N_5S$	60.18	5.72	23.40	...	...	60.10	5.57	23.20	...	...
274–274.5 dec.	$C_{16}H_{19}N_5S \cdot 2HCl \cdot 2H_2O$	45.49	5.97	16.58	16.80	7.59	45.06	5.81	16.32	16.50	8.12
201–203	$C_{15}H_{16}ClN_5S$	53.96	4.83	20.98	...	...	54.17	4.73	20.83	...	...
135–136	$C_{16}H_{18}ClN_5S$	55.24	5.21	20.13	...	...	55.42	5.40	19.70	...	...
133–134	$C_{15}H_{19}N_5S$	59.78	6.36	23.24	...	...	59.61	5.95	23.09	...	...

63.12; H, 6.62; N, 9.20. Found: C, 63.19; H, 6.68; N, 9.24. [b] Calcd. for H_2O, 5.76; found (K.F.), 6.5. [c] Arylthio derivative obtained as intractable gum; cyclized directly. [d] Over-all yield from 5-bromopyrimidine; arylthio derivative not isolated.

most of it. The yellow insoluble fraction consisted of 2.4 g. of **o,o′-diamino-p,p′-dichlorodiphenyl disulfide**, m.p. 115–117°.

Anal. Calcd. for $C_{12}H_{10}Cl_2N_2S_2$: C, 45.43; H, 3.18; N, 8.83. Found: C, 45.76; H, 3.35; N, 8.93.

On neutralization with acetic acid, the filtrate yielded a white precipitate, 10 g. (XXI). This melted at 226–228° after reprecipitation from alkali and crystallization from ethanol.

Cyclization of 5-(*o*-Aminoarylthio)-4-hydroxypyrimidines to 10*H*-Pyrimido[5,4-*b*][1,4]benzothiazines. (A) Direct Cyclization in the Presence of Acid.—The 5-(*o*-aminoarylthio)pyrimidines were mixed with approximately 20 volumes of 95% ethanol, and concentrated hydrochloric acid was added in an amount sufficient to produce a concentration of 0.2–1.2 *N* acid. Sometimes the pyrimidine precipitated as the hydrochloride salt, but in most instances it went into solution upon heating. The solutions were then heated on the steam bath under reflux for 6–24 hr. The colorless solutions or white precipitates gradually turned a bright yellow and sometimes precipitated the yellow hydrochloride salts of the product from the hot solutions. In other instances, the hydrochlorides precipitated upon cooling, or upon concentrating and cooling. These were isolated and usually slurried in dilute sodium hydroxide to remove any starting material or byproducts. The pyrimidobenzothiazines, including the 2-hydroxy derivatives, remained insoluble in alkaline media at room temperature, and the color soon changed from the bright yellow of the hydrochloride salts to a pale cream. The free bases were sometimes gummy at first, but soon crystallized. They were then isolated, washed well with water, and recrystallized, usually from ethanol or 2-methoxyethanol. Most of the pyrimidobenzothiazines were readily soluble in organic media. This was not true of the 2-hydroxy derivatives, however, which were exceedingly insoluble in almost all types of solvent. They showed slight solubility in hot dimethyl sulfoxide and hot sodium hydroxide, and could be dissolved in warm alcoholic hydrochloric acid, but not dilute aqueous acid. The 2-amino-4-hydroxy derivative did dissolve easily in acid and alkali, however.

Some of the free bases, particularly those with a 2-amino group, were unstable to light and rapidly assumed a reddish hue. On paper chromatography these compounds were converted to two and three component mixtures which contained none of the original pyrimidobenzothiazines, as determined by spectrophotometry. The hydrochloride salts were usually more stable to storage. The 2-amino-4-hydroxy derivative was particularly unstable. It rapidly turned from bright yellow to a dark green upon filtering as the hydrochloride salt. It was difficult to obtain reasonable analytical data (XXXII); the ultraviolet spectrum indicated the probable identity as a pyrimidobenzothiazine, however.

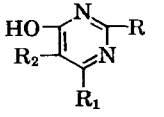
The pyrimidobenzothiazines which were prepared by this procedure are characterized in Table V. Specific examples are described subsequently.

2-Amino-10*H*-pyrimido[5,4-*b*][1,4]benzothiazine Hydrochloride (XXIX).—A mixture of 16 g. (0.069 mole) of 2-amino-4-hydroxy-5-(*o*-aminophenylthio)pyrimidine, 320 ml. of 95% ethanol, and 32 ml. (0.38 mole) of concentrated hydrochloric acid was heated under reflux for 6 hr. The pyrimidine slowly dissolved, producing a clear yellow solution. Upon cooling, long yellow needles separated; 12.2 g. (dry). The filtrate was diluted with water and made alkaline with sodium hydroxide; an additional precipitate, 1.86 g., was thus obtained. The yellow hydrochloride salt was treated with alkali to remove any possible starting material. The substance turned from yellow to a light cream color during this treatment. This free base was identical with the aforementioned precipitate from the mother liquor; both melted at 235°. They were combined and recrystallized from a mixture of 360 ml. of ethanol, 25 ml. of water, and 15 ml. of concentrated hydrochloric acid in the presence of charcoal. On chilling, long bright yellow needles (XXIX) were obtained; 11.0 g., m.p. 236–238°.

2-Hydroxy-10*H*-pyrimido[5,4-*b*][1,4]benzothiazine (XXVII).—A mixture of 14.7 g. (0.0625 mole) of 2,4-dihydroxy-5-(*o*-aminophenylthio)pyrimidine, 300 ml. of 95% ethanol, and 30 ml. of concentrated hydrochloric acid (0.36 mole) was heated on the steam bath for 16 hr. under reflux. Initially, practically all of the pyrimidine dissolved in the acid solution at room temperature, giving a transitory reddish color, and then precipitated almost immediately as the white hydrochloride salt. Upon con-

TABLE VI

ULTRAVIOLET ABSORPTION SPECTRA OF 4-HYDROXYPYRIMIDINES



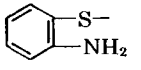
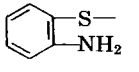
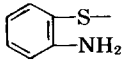
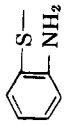
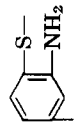
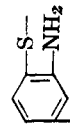
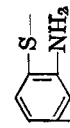
Compound	R	R_1	R_2	0.1 *N* HCl				Ethanol				0.1 *N* NaOH			
				λ_{max}, mμ	ε × 10^{-3}	λ_{min} mμ	ε × 10^{-3}	λ_{max} mμ	ε × 10^{-3}	λ_{min} mμ	ε × 10^{-3}	λ_{max} mμ	ε × 10^{-3}	λ_{min} mμ	ε × 10^{-3}
I	$(CH_2)_5N$—	H	H	228	15.4	252	5.6	230	16.5	251	1.9	237	13.2	228	12.7
				267	6.9			301	7.6			283	5.5	266	3.6
II	$CH_2CH_2OCH_2CH_2N$—	H	H	228	14.6	254	5.7	228	14.4	252	2.1	232 sh	11.4	261	3.5
				265	6.3			298	6.6			281	5.7		
III	$CH_2CH_2OCH_2CH_2N$—	CH_3	H	232.5	14.5	256	6.5	230	13.6	257.5	2.8	240	11.3	232	11.1
				265	6.8			295	8.9			280	6.4	263	4.6
IV	$CH_3N(CH_2CH_2)_2N$—	H	H	225 sh	17.1	252	3.9	229	15.0	259	2.2	234 sh	12.3	262	3.5
				264	4.3			297	6.3			281	5.9		
V	$CH_3N(CH_2CH_2)_2N$—	CH_3	H	229	15.8	223	15.6	230	13.7	258	2.4	240	12.3	231	11.8
				268	5.5	252	4.4	295	9.0			281	6.4	264	4.6
VII	$(CH_3)_2N$—	CH_3	Br	234	14.0	259	5.2	233	12.6	266	1.6	238	14.2	225	12.9
				280	7.7			310	11.7			296	6.4	272	3.3
VIII	$(CH_2)_5N$—	H	Br	236	17.6	253	5.0	235	15.2	272	2.1	242	15.0	274	3.3
				285	7.6			318	10.4			297	6.1		
IX	$(CH_2)_5N$—	CH_3	Br	240	16.2	265	6.5	238	13.2	268	1.6	244	14.8	228	12.5
				283	7.9			313	11.4			296	6.3	275	4.3
X	$CH_2CH_2OCH_2CH_2N$—	H	Br	237	16.9	265	4.9	235	13.2	269	1.7	239	13.3	228	12.6
				282.5	6.3			312.5	9.4			295	6.2	270	3.2
XI	$CH_2CH_2OCH_2CH_2N$—	CH_3	Br	240	15.9	267	6.2	237.5	12.3	267.5	1.9	242	13.3	228	12.3
				281	7.0			308	10.4			290	7.0	270	4.4
XII[a]	$CH_3N(CH_2CH_2)_2N$—	H	Br	228	18.9	265	3.5	236	15.0	268	2.8	240	14.5	228	15.4
				290 sh	4.2			308	8.0			295	6.7	270	3.5
				308	4.3										
XIII[a]	$CH_3N(CH_2CH_2)_2N$—	CH_3	Br	227	17.7	265	4.8	237	14.7	267	3.2	242	14.5	228	13.8
				280	5.1			303	8.7			292	7.1	270	4.7
				300 sh	4.4										
XIV[a]	$(CH_3)_2N(CH_2)_3NH$—	H	Br	227	12.3	255	3.6	228	9.6	260	1.1	235 sh	11.7	265	2.5
				278	6.5			305	7.1			293	6.5		
XV	OH	H		274	7.55	245	6.22	294[b]	6.4	270[b]	6.0	296	11.0	265	4.8
												297[c]	11.3	265[c]	4.6
XLV	OH	H	C_6H_5S—	244	12.8	225	9.0	246	12.1	226	8.5	243	14.1	232	12.8
				270 sh	7.5			270 sh	7.8			288	10.2	266	7.2
				298 sh	3.6			298 sh	3.6						
XVII	NH_2	H		233	10.5	225	10.4	...	..	...	...	235 sh	15.6	268	6.2
				275 sh	7.1							292	9.7		
XIX	NH_2	OH		255	18.5	...	...	...	..	...	...	255[d]	16.7	233[d]	13.6
												290 sh[d]	5.5		
XX	$(CH_3)_2N$—	CH_3		235 sh	21.8							249[d]	20.4	240[d]	20.0
				280 sh	9.8	...	...	...	..	...	...	297[d]	12.9	277[d]	9.4

TABLE VI (*Continued*)

Compound	R	R¹	R²	0.1 *N* HCl λ_{max} mμ	0.1 *N* HCl $\epsilon \times 10^{-3}$	0.1 *N* HCl λ_{min} mμ	0.1 *N* HCl $\epsilon \times 10^{-3}$	Ethanol λ_{max} mμ	Ethanol $\epsilon \times 10^{-3}$	Ethanol λ_{min} mμ	Ethanol $\epsilon \times 10^{-3}$	0.1 *N* NaOH λ_{max} mμ	0.1 *N* NaOH $\epsilon \times 10^{-3}$	0.1 *N* NaOH λ_{min} mμ	0.1 *N* NaOH $\epsilon \times 10^{-3}$
XXI	$-(CH_2)_5N-$	H		235 sh	25.9	...	...	...	...	...	...	252[d]	20.7	238[d]	20.0
				285 sh	11.1							303[d]	13.3	283[d]	7.4
XXII	$-(CH_2)_5N-$	CH_3		239 sh	23.2	...	...	...	...	...	...	256[d]	20.5	242[d]	18.6
				280 sh	11.6							303[d]	13.3	282[d]	9.2
XXIII	$-CH_2CH_2OCH_2CH_2N-$	H		240 sh	20.6	...	...	...	...	...	...	249[d]	19.0	238[d]	18.3
				288 sh	8.5							302[d]	12.8	278[d]	8.5
XXV	$CH_3N(CH_2CH_2)_2N-$	H		218	24.2	280	6.9	...	...	...	...	250	19.0	240	18.3
				242 sh	18.1							302	12.7	278	7.3
				305	8.9							250[d]	21.5	242[d]	21.1
				223[e]	25.2	...	...					302.5[d]	14.0	278[d]	9.1
				242 sh[e]	20.8										
				280 sh[e]	10.4										

[a] As hydrobromide salt. [b] In pH 5.75 phosphate buffer. [c] In pH 9.48 glycine–NaOH buffer. [d] In pH 11.0 glycine–NaOH buffer. [e] In 1 *N* HCl.

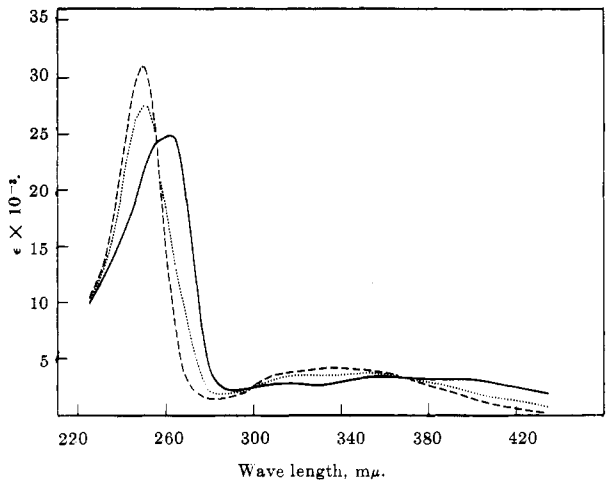


Fig. 1.—Ultraviolet absorption spectrum of 10*H*-pyrimido-[5,4-*b*][1,4]benzothiazine: ———pH 1.08; .....pH 4.04; — — — pH 7.02.

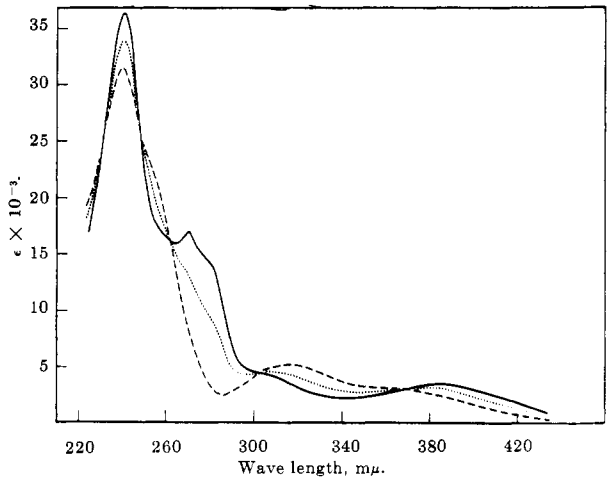


Fig. 2.—Ultraviolet absorption spectrum of 2-amino-10*H*-pyrimido[5,4-*b*][1,4]benzothiazine: ——— pH 1.09; ..... pH 5.50; — — — pH 8.02.

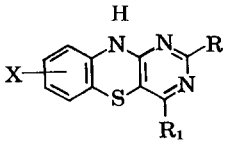
tinued heating, the nature of the precipitate changed, becoming gradually yellow. At the end of the heating period, a matte of yellow needles was present. After chilling, the product, 13.8 g., was isolated. This appeared to be a mixture of bright yellow and almost white crystals. The mixture was heated in dilute ammonia; most of the substance remained insoluble, but changed color to a lighter yellow. It was filtered hot, treated once more with ammonia, and washed well with water; yield (XXVII), 10.2 g. (dry), m.p. *ca.* 380°. The substance was found to dissolve in hot sodium hydroxide solution containing ethanol. It precipitated on cooling as a yellow sodium salt which changed crystal form on washing well with water and reverted to the un-ionized hydroxypyrimidobenzothiazine. It also dissolved in hot 1 *N* hydrochloric acid in ethanol and crystallized as yellow needles on cooling.

The soluble fraction from the ammonia extraction was neutralized with acid; this precipitated white crystals (1 g.) which had the ultraviolet spectrum of the starting material (XV).

Cyclizations of 5-(*o*-Aminoarylthio)pyrimidines with Phosphoryl Chloride.—Two grams of 2-amino-4-hydroxy-5-(*o*-aminophenylthio)pyrimidine was boiled with 20 ml. of phosphoryl chloride until all was dissolved (1 hr.). Excess phosphoryl chloride was removed by distillation. The residue was poured on ice and neutralized with ammonia. A yellow precipitate was isolated. This was slurried in hot ethanol, in which it was practically insoluble, filtered, and washed with ethanol and ether. This substance (1.4 g.) was insoluble in acid, but, on warming with 0.2 *N* sodium hydroxide to 60°, most of it dissolved. It was filtered from gray insoluble material (0.4 g.), and neutralized to pH 4, which yielded a yellow precipitate (0.66 g.). This substance did

TABLE VII

ULTRAVIOLET ABSORPTION SPECTRA OF 10*H*-PYRIMIDO[5,4-*b*][1,4]BENZOTHIAZINES



Compound	R	R_1	X	Acidic media: Solvent	Acidic media: λ_{max} mμ	Acidic media: $\epsilon \times 10^{-3}$	Acidic media: λ_{min} mμ	Acidic media: $\epsilon \times 10^{-3}$	Neutral or alkaline media: Solvent	Neutral or alkaline media: λ_{max} mμ	Neutral or alkaline media: $\epsilon \times 10^{-3}$	Neutral or alkaline media: λ_{min} mμ	Neutral or alkaline media: $\epsilon \times 10^{-3}$
LVI	H	H	...	0.1 *N* HCl	261	24.8	288	2.1	pH 7.02 (phosphate)	249	30.8	280	1.5
					315	2.8				340	4.1		
					360	3.4							
LVII	H	H	8-Cl	1 *N* HCl	263	31.0	225	9.0	pH 7.01 (hosphate)	253	35.7	228	17.5
					320 sh	3.3	292	1.6		327	4.7	280	0.98
					360	4.0			95% EtOH	253	39.6	229	13.0
										327	5.4	285	1.3
XLVI	Cl	H	...	1 *N* HCl in 50% EtOH	255	27.5	225	10.2	95% EtOH	251	32.2	285	0.85
					325	3.3	290	1.7		350	4.2		
					360	4.2	335	3.2					
XLVII	Cl	H	8-Cl	1 *N* HCl in 50% EtOH	256	31.6	228	12.2	95% EtOH	255	33.8	228	11.5
					335	4.0	292	1.6		335	4.4	285	1.0
LIV	CH_3O—	H	...	0.1 *N* HCl	237	25.2	250	16.4	pH 11 (glycine–NaOH)	237.5	26.3	244	23.8
					255 sh	16.7	287	1.2		251	24.4		
					263	18.9	350	1.4		312	4.9	280	2.1
					274 sh	12.5				355 sh	3.9		
					315	2.5							
					395	3.4							
LV	$CH_3OCH_2CH_2O$—	H	...	0.1 *N* HCl	237	25.6	251	18.5	95% EtOH	239	24.6	246	23.0
					256 sh	18.8	288	2.8		252	24.4	280	1.3
					264	20.4	350	2.5		320	4.9		
					274 sh	14.1				360 sh	3.6		
					310	4.1							
					395	4.1							
XXVII	OH	H	...	0.02 *N* HCl[a] in 50% EtOH	237	24.6	263	12.6	0.1 *N* NaOH	237	27.6	285	4.0
					255 sh	14.6	340	2.0		255 sh	17.4		
					270	13.4				309	6.1		
					280 sh	11.7				355 sh	2.8		
					305 sh	4.5							
					375	3.3							
				1 *N* HCl[a]	230	21.6	247	9.9	2 *N* NaOH	226	43.5	285	3.6
					257 sh	13.4	293	4.7		254 sh	17.4		
					267	14.6	345	0.85		310	6.1		
					305	5.2				350 sh	3.6		
					415	3.7							

TABLE VII (*Continued*)

Compound	R	R_1	X	Acidic media: Solvent	λ_{max} mμ	$\epsilon \times 10^{-3}$	λ_{min} mμ	$\epsilon \times 10^{-3}$	Neutral or alkaline media: Solvent	λ_{max} mμ	$\epsilon \times 10^{-3}$	λ_{min} mμ	$\epsilon \times 10^{-3}$
XXIX	NH_2	H	...	0.1 *N* HCl	241	36.2	264	15.8	pH 8.02 (phos-	240	31.4	225	20.0
					260 sh	16.6	342	2.2	phate)	255 sh	21.7	286	2.5
					270	17.0				315	5.3		
					280 sh	14.2				360 sh	3.2		
					300 sh	4.6			50% EtOH	242	31.6	225	20.4
					385	3.5				255 sh	22.4	288	2.4
										317	5.6		
										360 sh	3.2		
XXX	NH_2	H	8-Cl	0.1 *N* HCl	241	38.2	352	2.1	95% EtOH	243	32.2	290	2.3
					260 sh	25.2				260 sh	26.1		
					270 sh	21.5				320	7.0		
					320 sh	3.9				360 sh	3.1		
					385	3.2							
XXXI	NH_2	H	7,8-$(CH_3)_2$	0.1 *N* HCl	243	41.3	269	16.6	95% EtOH	244	36.2	292	2.2
					273	17.4	345	2.5		320	5.6		
					284 sh	14.9				360 sh	3.4		
					310 sh	4.5							
					388	4.2							
XXXII	NH_2	OH	...	0.1 *N* HCl	253	40.0	360	2.2	pH 11 (glycine–	255	46.0	...	...
					280 sh	14.3			NaOH)	350 sh	2.9		
					310 sh	5.7							
					375	2.3							
LI	NH_2NH—	H	...	0.1 *N* HCl	244	33.8	345	2.5	95% EtOH	247	33.8	228	17.6
					268 sh	16.8				322	5.4	295	3.3
					280 sh	14.1				360 sh	3.0		
					310 sh	5.1							
					385	3.3							
LII	NH_2NH—	H	8-Cl	0.1 *N* HCl	246	34.2	226	18.1	95% EtOH	225	24.4	232	23.4
					280 sh	16.8	350	2.1		251	31.4	295	3.3
					310 sh	5.3				322	6.3		
					385	2.7				365 sh	2.7		
LIII	SH	H	...	(Unstable)	...	..	...	...	0.1 *N* NaOH	274	26.6	240	15.2
										338	6.0	314	5.3
XXXIII	$(CH_3)_2N$—	CH_3	...	0.1 *N* HCl	249	37.8	265	16.9	pH 11 (glycine–	261	31.3	296	4.1
					280	22.2	340	2.3	NaOH)	320	6.1		
					380	3.5				370 sh	2.3		
XXXIV	$\ulcorner(CH_2)_5N$—	H	...	0.1 *N* HCl	253	46.8	272	16.2	95% EtOH	255	44.1	303	6.1
					285	18.5	347	2.6		320	7.4		
					383	4.0				360 sh	3.4		
XXXV	$\ulcorner(CH_2)_5N$—	H	8-Cl	0.1 *N* HCl	255	49.6	275	18.5	95% EtOH	257	42.8	302	5.7
					290	21.4	350	1.9		325	7.4		
					385	3.2							
XXXVI	$\ulcorner(CH_2)_5N$—	CH_3	8-Cl	0.1 *N* HCl	220	20.4	229	15.7	95% EtOH	231	26.6	241	19.9
					254	38.7	271	19.0		259	32.3	297	3.3
					285	23.3	350	1.8		325	7.5		
					390	2.0							

TABLE VII (*Continued*)

Compound	R	R_1	X	Acidic media: Solvent	Acidic media: λ_{max} mμ	Acidic media: $\epsilon \times 10^{-3}$	Acidic media: λ_{min} mμ	Acidic media: $\epsilon \times 10^{-3}$	Neutral or alkaline media: Solvent	Neutral or alkaline media: λ_{max} mμ	Neutral or alkaline media: $\epsilon \times 10^{-3}$	Neutral or alkaline media: λ_{min} mμ	Neutral or alkaline media: $\epsilon \times 10^{-3}$
XXXVII	$-CH_2CH_2OCH_2CH_2N-$	H	...	0.1 *N* HCl	251	43.5	272	16.2	95% EtOH	253	41.2	299	3.1
					281	18.1	344	2.0		328	6.1		
					385	3.4				360 sh	3.4		
XXXVIII	$-CH_2CH_2OCH_2CH_2N-$	H	8-Cl	0.1 *N* HCl	252	51.2	275	23.1	95% EtOH	255	43.2	236	24.4
					282	24.7	350	2.9		325	8.0	298	4.2
					385	4.0				360 sh	3.2		
XXXIX	$-CH_2CH_2OCH_2CH_2N-$	CH_3	8-Cl	0.1 *N* HCl	251	47.5	228	33.1	95% EtOH	257	37.5	238	22.4
					283	30.5	270	25.7		327	8.4	294	3.7
					385	4.0	350	3.0					
XL	$CH_3N(CH_2CH_2)_2N-$	H	...	0.1 *N* HCl	245	38.0	269	17.2	95% EtOH	253	38.4	298	3.5
					276	18.7	345	2.4		322	5.8		
					310 sh	6.2				360 sh	2.8		
					385	3.6							
XLI	$CH_3N(CH_2CH_2)_2N-$	CH_3	...	0.1 *N* HCl	247	40.5	265	21.4	pH 11 (glycine–NaOH)	253	35.4	296	3.6
					275	26.6	350	2.5		324	6.4		
					310 sh	7.3				360 sh	2.1		
					385	3.6							
XLII	$CH_3N(CH_2CH_2)_2N-$	H	8-Cl	0.1 *N* HCl	249	43.4	270	22.2	95% EtOH	235 sh	25.7	298	3.9
					277	23.8	350	2.1		256	42.6		
					390	3.0				326	7.4		
										370 sh	2.3		
XLIII	$CH_3N(CH_2CH_2)_2N-$	CH_3	8-Cl	0.1 *N* HCl	248	44.0	270	28.2	95% EtOH	258	40.0	290	2.4
					278	31.8	355	2.4		325	8.7		
					385	3.5							
XLIX	$(CH_3)_2N(CH_2)_2NH-$	H	...	0.1 *N* HCl	243	36.3	267	16.9	95% EtOH	247	36.1	228	18.7
					260 sh	18.6	350	2.1		320	5.9	295	3.3
					272	18.2				365 sh	3.0		
					283 sh	16.0							
					310 sh	5.2							
					385	3.5							
XLIV	$(CH_3)_2N(CH_2)_3NH-$	H	...	0.1 *N* HCl	242	38.0	268	15.1	pH 11 (glycine–NaOH)	245	36.8	292	3.8
					275	16.3	345	2.0		317	5.5		
					285 sh	13.7				360 sh	3.2		
					305 sh	6.0							
					385	3.2							
L	$CH_3N(CH_2CH_2)_2N(CH_2)_3NH-$	H	8-Cl	0.1 *N* HCl	246	34.0	350	1.9	95% EtOH	232	44.0	238	39.6
					265 sh	22.0				248	48.0	298	5.9
					280 sh	18.0				322	8.7		
					390	3.1							

[a] Sample dissolved in 1 *N* HCl in 87% EtOH, and diluted 1:50 into solvent systems.

not have a sharp melting point, but gradually softened between 220–240°. It was insoluble in ethanol, glycol, dimethylformamide, and acetic acid, but soluble in boiling dimethyl sulfoxide. Its ultraviolet absorption spectrum had maxima identical with the maxima of 2-amino-10*H*-pyrimido[5,4-*b*][1,4]benzothiazine (XXIX), but with only 70% the intensity. Indications were that this was a phosphoramide of the desired product.

Anal. Calcd. for $C_{10}H_9N_4O_3PS \cdot 0.5H_2O$: C, 39.34; H, 3.30; N, 18.35. Found: C, 39.11; H, 3.50; N, 18.05.

The experiment was then repeated with acetylation prior to reaction with phosphoryl chloride. One gram of 2-amino-4-hydroxy-5-(*o*-aminophenylthio)pyrimidine was mixed with 20 ml. of acetic anhydride and 0.1 ml. of pyridine and heated on the steam bath for 45 min. It did not dissolve, so it was heated to the boiling point for 15 min. All but a trace dissolved. The mixture was filtered hot, and chilled. A white precipitate separated (1.0 g.), which was recrystallized from ethanol; m.p. 224–226°. Analyses indicated that this was a mixture. It was used in this form for the reaction which followed. This product, 0.75 g., was heated at the boiling point with 15 ml. of phosphoryl chloride for 30 min., followed by isolation as before. A pale yellow product was isolated. This was heated with 1 *N* hydrochloric acid in ethanol for an hour to remove acetyl groups, and made alkaline, which resulted in the precipitation of 0.29 g. of pale yellow product. Upon recrystallization from ethanol, it melted at 235° and was identical with the 2-amino-10*H*-pyrimido[5,4-*b*][1,4]benzothiazine (XXIX).

2-Chloro-10*H*-pyrimido[5,4-*b*][1,4]benzothiazine (XLVI).—Twenty grams of 2-hydroxy-10*H*-pyrimido[5,4-*b*][1,4]benzothiazine was heated under reflux with 300 ml. of phosphoryl chloride for 5 hr. At the end of this time, the solution contained a dark red precipitate. This was isolated after cooling (6.4 g.). The filtrate was then concentrated to remove excess phosphoryl chloride, poured on ice, and neutralized with sodium carbonate. A yellow precipitate (14.0 g.) separated, which was isolated and dried. Upon sublimation, this yielded 10.2 g. of long yellow needles, which were purified further by recrystallization from 2-methoxyethanol. Bright yellow needles were obtained; m.p. 281–284° dec.

Anal. Calcd. for $C_{10}H_6ClN_3S$: C, 50.96; H, 2.57; N, 17.83; Cl, 15.04. Found: C, 50.82; H, 2.54; N, 18.11; Cl, 15.20.

It was found later that a product of satisfactory purity could be obtained without sublimation, by recrystallizing two or three times from 2-methoxyethanol. The red precipitate formed in the reaction mixture did not yield 2-chloro-10*H*-pyrimido[5,4-*b*][1,4]-benzothiazine upon treatment with alkali. A small portion of the alkali-treated material was soluble in hot 2-methoxyethanol; this yielded a precipitate on cooling, which did not melt when heated to 350°. The substance was not investigated further.

2,8-Dichloro-10*H*-pyrimido[5,4-*b*][1,4]benzothiazine (XLVII). 2-Hydroxy-8-chloro-10*H*-pyrimido[5,4-*b*][1,4]benzothiazine was chlorodehydroxylated in a manner similar to that described before to yield XLVII. This was formed as bright yellow needles, m.p. 289–291°, upon recrystallization from 2-methoxyethanol.

Anal. Calcd. for $C_{10}H_5Cl_2N_3S$: C, 44.46; H, 1.83; N, 15.55; Cl, 26.25. Found: C, 44.63; H, 1.95; N, 15.20; Cl, 25.75.

2-Chloro-7,8-dimethyl-10*H*-pyrimido[5,4-*b*][1,4]benzothiazine (XLVIII).—This compound was prepared by treating crude 2-hydroxy-7,8-dimethyl-10*H*-pyrimido[5,4-*b*][1,4]benzothiazine with phosphoryl chloride, as before. It melted at 253–255° after several recrystallizations from 2-methoxyethanol.

Anal. Calcd. for $C_{12}H_{10}ClN_3S$: C, 54.64; H, 3.82; N, 15.93. Found: C, 54.32; H, 3.90; N, 15.49.

2-(3-Dimethylaminopropylamino)-10*H*-pyrimido[5,4-*b*][1,4]-benzothiazine (XLIV).—This compound, which was prepared by complete synthesis (see Table V) was also prepared from the corresponding 2-chloro derivative XLVI. A mixture of 5.0 g. of XLVI and 25 ml. of 3-dimethylaminopropylamine was heated in an oil bath at 140–150° for 2 hr., which yielded a clear solution. Excess amine was removed by distillation, and the residue treated with water. A gum formed which solidified on standing (5.5 g.). This was recrystallized twice from dilute ethanol, which yielded pale yellow crystals, m.p. 130–131°.

Anal. Calcd. for $C_{15}H_{19}N_5S$: C, 59.78; H, 6.36; N, 23.24. Found: C, 59.37; H, 6.08; N, 22.89.

2-(2-Dimethylaminoethylamino)-10*H*-pyrimido[5,4-*b*][1,4]-benzothiazine (XLIX).—This compound was prepared from 2-chloro-10*H*-pyrimido[5,4-*b*][1,4]benzothiazine plus 2-dimethylaminoethylamine by the procedure described in the preceding section. The product crystallized with difficulty. Upon recrystallization from dilute ethanol, a yellow product was formed; m.p. 143–144°.

Anal. Calcd. for $C_{14}H_{17}N_5S$: C, 58.51; H, 5.96; N, 24.37. Found: C, 58.43; H, 5.75; N, 24.26.

2-[3-(4-Methylpiperazinyl)propylamino]-8-chloro-10*H*-pyrimido-[5,4-*b*][1,4]benzothiazine (L).—A mixture of 2.3 g. of 2,8-dichloro-10*H*-pyrimido[5,4-*b*][1,4]benzothiazine and 10 ml. of 1-methyl-4-(3-aminopropyl)piperazine was heated in an oil bath at 150° for 1.5 hr. A clear yellow solution was formed which yielded a solid crystalline mass on cooling. This was slurried in dilute sodium hydroxide and the precipitate isolated (3.3 g.). Upon recrystallization from ethanol with the aid of charcoal a light yellow product was obtained; m.p. 180°.

Anal. Calcd. for $C_{18}H_{23}ClN_6S$: C, 55.30; H, 5.93; N, 21.50. Found: C, 54.86; H, 5.74; N, 21.62.

2-Hydrazino-10*H*-pyrimido[5,4-*b*][1,4]benzothiazine (LI).—A 14.8-g. sample of 2-chloro-10*H*-pyrimido[5,4-*b*][1,4]benzothiazine was dissolved in 600 ml. of hot 2-methoxyethanol. To this was added 48 ml. of hydrazine hydrate over a 5-min. period. A shiny yellow precipitate formed almost immediately. The mixture was refluxed for 30 min., cooled, filtered, and washed well with 2-methoxyethanol and ethanol. There was obtained 13.4 g. (92.5%) of the hydrazino derivative. A 0.25-g. sample of this was recrystallized from 50 ml. of 2-methoxyethanol; m.p. 285–287°.

Anal. Calcd. for $C_{10}H_9N_5S$: C, 51.93; H, 3.92; N, 30.28. Found: C, 51.81; H, 3.73; N, 29.66.

2-Hydrazino-8-chloro-10*H*-pyrimido[5,4-*b*][1,4]benzothiazine (LII).—2,8-Dichloro-10*H*-pyrimido[5,4-*b*][1,4]benzothiazine was treated in the previously described manner with hydrazine hydrate to yield the 2-hydrazino derivative, m.p. 279–281°, after recrystallization from 2-methoxyethanol.

Anal. Calcd. for $C_{10}H_8ClN_5S$: C, 45.20; H, 3.03; N, 26.36. Found: C, 45.62; H, 3.23; N, 26.72.

2-Mercapto-10*H*-pyrimido[5,4-*b*][1,4]benzothiazine (LIII).

(A) From 2-Chloro-10*H*-pyrimido[5,4-*b*][1,4]benzothiazine (XLVI).—A mixture of 0.50 g. (0.00212 mole) of XLVI, 0.161 g. (0.00212 mole) of thiourea, and 20 ml. of 2-methoxyethanol was heated under reflux for 3 hr. A yellow precipitate formed which was filtered from the hot solution and washed with 2-methoxyethanol and ethanol (0.22 g., m.p. 272–274° dec.). No additional precipitate was formed by chilling the filtrate. This product was found to be extremely insoluble in most solvents. Upon determination of the ultraviolet absorption spectrum in alkali (pH 11 and 13), it was found that the substance was quite unstable in these media. Warming of the solution for 5 min. on the steam bath caused a marked lowering of the maxima. The substance was also unstable in acid.

Anal. Calcd. for $C_{10}H_7N_3S_2$: C, 51.48; H, 3.02; N, 18.01. Found: C, 51.10; H, 2.96; N, 17.76.

(B) From 5-Bromo-2-thiouracil.—A mixture of 2.2 g. (0.01 mole of 5-bromo-2-thiouracil,[21] 2.76 g. (0.02 mole) of potassium carbonate, 1.3 g. (0.01 mole) of *o*-aminothiophenol, and 20 ml. of glycol was heated under nitrogen to 140° for 30 min., and allowed to cool slowly. A clear solution was formed. The mixture was poured into water, yielding an oil which was removed by extraction with ether. The aqueous solution was neutralized, which resulted in the slow formation of a small precipitate. This was isolated and washed well with alcohol and ether. The light gray residue weighed 80 mg.; m.p. 213–224°. This crude product was treated directly with 5 ml. of ethanol plus 0.15 ml. of concentrated hydrochloric acid. Upon heating on the steam bath, the solution soon turned yellow. After 21 hr. a yellow precipitate was present. This was isolated and washed well with water, ethanol, and ether. The product (40 mg.) melted at 275–280° dec. Its spectral properties were identical in alkaline medium with those of the product of procedure A.

2-Methoxy-10*H*-pyrimido[5,4-*b*][1,4]benzothiazine (LIV).—A mixture of 5.0 g. (0.0212 mole) of 2-chloro-10*H*-pyrimido[5,4-*b*]-[1,4]benzothiazine, 1.25 g. (0.023 mole) of sodium methylate, and 100 ml. of methanol was heated under reflux for 18 hr. The chloro compound was not very soluble in this medium, and reacted slowly. A yellow precipitate was present in the hot solution at the end of the heating period. This was filtered off and washed with water; weight, 2.46 g. The filtrate was cooled, yielding 1.53 g. of light yellow precipitate. The mother liquor yielded an additional 0.38 g. upon adding water. These fractions were all found

(21) H. W. Barrett, I. Goodman, and K. Dittmer, *J. Am. Chem. Soc.*, **70**, 1753 (1948).

to melt between 202–203°; combined weight, 4.17 g. Recrystallization from methanol produced long yellow needles, m.p. 204.5–205°.

Anal. Calcd. for $C_{11}H_9N_3OS$: C, 57.12; H, 3.92; N, 18.17. Found: C, 57.46; H, 3.58; N, 17.80.

2-(2-Methoxyethoxy)-10*H*-pyrimido[5,4-*b*][1,4]benzothiazine (LV).—In efforts to convert 2-chloro-10*H*-pyrimido[5,4-*b*][1,4]-benzothiazine to the parent unsubstituted derivative, the method of Albert and Royer[22] was investigated. This involves reaction of a chloro heterocycle with *p*-toluenesulfonhydrazide, followed by treatment of the resultant unstable hydrazide derivative with alkali to produce the unsubstituted heterocycle. Since the 2-chloropyrimidobenzothiazine was virtually unsoluble in the chloroform medium used by these workers, the reaction was tried in 2-methoxyethanol. Most of the starting material was recovered; however, starting from 0.5 g. of 2-chloro-10*H*-pyrimido-[5,4-*b*][1,4]benzothiazine, 75 mg. of a more soluble derivative was obtained, which was isolated by adding water to the 2-methoxyethanol solution. Upon recrystallization from ethanol, this compound melted at 166–167°. It was pale yellow, and dissolved in acid to give a bright yellow solution. Its ultraviolet absorption spectrum was virtually identical with that of 2-methoxy-10*H*-pyrimido[5,4-*b*][1,4]benzothiazine. It was concluded from the analysis that the compound was the 2-(2-methoxyethoxy) derivative.

Anal. Calcd. for $C_{13}H_{13}N_3O_2S$: C, 56.71; H, 4.76; N, 15.26. Found: C, 56.31; H, 4.55; N, 15.20.

10*H*-Pyrimido[5,4-*b*][1,4]benzothiazine[7] (LVI).—A 13.4-g. sample (0.058 mole) of 2-hydrazino-10*H*-pyrimido[5,4-*b*][1,4]-benzothiazine was slurried in 750 ml. of water and dissolved by the addition of 60 ml. of 2 *N* hydrochloric acid. This was warmed to 80°, and 400 ml. of a 10% aqueous solution of copper sulfate pentahydrate was added dropwise over a 15-min. period, with stirring. Nitrogen was evolved vigorously. Heating at 80° was continued for another 15 min., followed by 5 min. at the boiling point. A brown precipitate was formed, which was separated, washed with water, and dried (19.7 g.) This copper-containing product was slurried in about 400 ml. of ethanol plus a small amount of hydrochloric acid, warmed, and hydrogen sulfide bubbled in until saturation was reached. The black precipitate was isolated, and found to contain some brown lumps. After grinding, the hydrogen sulfide treatment was repeated twice. The combined alcoholic filtrates were then evaporated to dryness, which yielded a yellow–orange residue weighing 11.7 g. This was warmed in dilute hydrochloric acid, which caused all but a small amount of reddish material to dissolve. After clarifying, the solution was made alkaline, which resulted in the separation of a yellow–gray precipitate, 9.2 g. (dry). This proved to be a mixture of the 10*H*-pyrimidobenzothiazine and the original 2-hydrazino derivative. It was extracted with hot benzene to remove the product. Upon concentration and chilling of the benzene extracts, the product crystallized as pale yellow needles weighing 4.3 g., m.p. 180–181°. Further recrystallization from benzene did not raise the melting point.

Anal. Calcd. for $C_{10}H_7N_3S$: C, 59.68; H, 3.51; N, 20.88. Found: C, 59.67; H, 3.40; N, 20.63.

8-Chloro-10*H*-pyrimido[5,4-*b*][1,4]benzothiazine (LVII).—To a solution of 4.8 g. of 2,8-dichloro-10*H*-pyrimido[5,4-*b*]-[1,4]benzothiazine in 180 ml. of hot 2-methoxyethanol, was added 10 ml. of water plus 10 ml. of glacial acetic acid. Ten grams of zinc dust was slowly added to the well-stirred solution over a 3-hr. period. The zinc was then filtered from the warm solution, and the filtrate chilled overnight. A yellow precipitate (1.38 g.) separated. This proved to be a mixture consisting mainly of the starting material with a little product. Several volumes of water were added to the filtrate, which precipitated light yellow crystals, 3.0 g. This product was recrystallized from ethanol, which yielded yellow needles, m.p. 220–221°.

Anal. Calcd. for $C_{10}H_6ClN_3S$: C, 50.96; H, 2.57; N, 17.83. Found: C, 51.28; H, 2.41; N, 17.60.

Ultraviolet Absorption Spectra and p*Ka* Values.—Ultraviolet spectral determinations were made with a Beckman DU spectrophotometer. Stock solutions of compounds to be tested were normally prepared at concentrations of 25 to 50 mg./100 ml. in ethanol or other suitable solvent, followed by 1:50 dilution into the test solution. Buffers which were used included phosphate, Walpole acetate, Sorensen's glycine–hydrochloric acid and glycene–sodium hydroxide, and borax, as well as hydrochloric acid and sodium hydroxide of varying normalities. pH determinations were made on a Beckman Model G pH meter. For determination of pK_a values, the spectra were determined at seven or more pH values, to establish two points for each pure species and to obtain values clustering near the midpoints between. All optical density measurements when plotted against pH for a given wave length gave good sigmoid curves. Optical density values in the 250–300-mμ region only were used for pK_a calculations. Slit widths below this region were considered too wide for accuracy. The pK_a values were calculated from the formula

$$pK_a = pH - \log \frac{\epsilon a - \epsilon x}{\epsilon x - \epsilon b}$$[23]

where ϵa is the extinction value of the protonated species, ϵb is the value of the base, and ϵx is the value at the measured pH. The reported pK_a values represent averages from determinations at 3 wave lengths selected in the areas of greatest spectral differences. Individual pK_a values obtained from the midpoints of the sigmoid curves were all within 0.1 pH unit of those calculated.

Acknowledgment.—The authors gratefully acknowledge the continued advice and encouragement of Dr. George H. Hitchings throughout the course of this investigation. The senior author wishes to express her indebtedness to Dr. J. F. Bunnett of Brown University for his valuable advice and suggestions. Thanks are also offered to P. R. W. Baker and his staff at the Wellcome Research Laboratories, Beckenham, Kent, England, for the microanalyses.

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Some New Syntheses of Amino- and Alkylaminopyrimidines and -pteridines

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Received April 15, 1963

The fusion of ammonium acetate or alkylammonium acetates with certain 2-methylthiopyrimidines and -pteridines has been found to be a convenient method for the preparation of the corresponding 2-amino or 2-alkylamino derivatives. The utilization of these same reagents also has led to some interesting selective amine exchange reactions.

The preparation of 2- and 4-aminopyrimidines and condensed pyrimidines by the reaction of amines with the corresponding mercapto and alkylthio derivatives has long been utilized in heterocyclic chemistry.[1] Many of these reactions require rather strenuous conditions and are usually carried out in a bomb except when high boiling amines are used. We have found that in many instances the same results can be obtained by utilizing the acetate salt of the appropriate amine in a

(1) For a recent discussion of these reactions in the pyrimidine series, see D. J. Brown, "The Pyrimidines," Interscience Publishers, Inc., a division of John Wiley and Sons, Inc., New York, N. Y., pp. 284 and 289.