0.97 at 21.0° and 0.78 at 29.6°. Equation 6 also explains why a plot of log k_2 *vs.* $1/T$ should give a combined value including ΔH_{ion} of $RSH \rightleftarrows RS^- + H^+$ and E_a for reaction of NPA with RS^-.

It appears that eq. 1 adequately describes the experimental data and that the attack on NPA is by RS^- which is shown to be a strong nucleophile. Formation of thiol ester as one of the products is supported by spectrophotometric data. Evidence for formation of thiol ester was found only at the lower *p*H values and at low, nearly equal, concentrations of reactants indicating that the thiol ester is hydrolyzed quite rapidly. Thiol esters which contain a hydroxyl or amine group in a suitable position would be expected to also be split by intramolecular attack by these groups[17,18] as well as by hydroxide ion catalysis. Rate of reaction was also found to be independent of ionic strength (up to 0.50; above this it decreased slowly) as would be expected from eq. 1. The reaction cannot be carried out in the presence of acetone because of its inhibition of the reaction.

(17) W. P. Jencks, S. Cordes and J. Carriuolo, *J. Biol. Chem.*, **235**, 3608 (1960).

(18) T. Wieland, W. Schafer and E. Bokelmann, *Ann. Chem.*, **573**, 99 (1951).

[CONTRIBUTION FROM THE CHEMICAL RESEARCH DIVISION OF G. D. SEARLE AND CO., CHICAGO 80, ILL.]

The Rearrangement of Sulfoxides of Pyrimido[5,4-b][1,4]thiazines

BY ELMER F. SCHROEDER AND R. M. DODSON[1]

RECEIVED DECEMBER 7, 1961

The crystallization of the pyrimidothiazine-5-oxide (IV) from methyl alcohol, ethyl alcohol or acetic acid produced the corresponding 6-methoxy-, 6-ethoxy- or 6-acetoxypyrimidothiazine (VIIIb, a, or d). When IV was stirred with water or allowed to stand at room temperature in the crystalline state, it was rearranged to the corresponding 6-hydroxy compound VIIIc. The course of this rearrangement was established by the conversion of VIIIa, *via* the amide XIIIa, and desulfurization with Raney nickel, to 1-propyl-3-ethyl-6-aminouracil (XIV) and ethoxyacetamide (XV). The rearranged products VIIIa, b, c, d and XIa were also independently synthesized from the corresponding 6-halo- or 6,6-dihalopyrimidothiazines IXa, b, c. The 6-ethoxypyrimidothiazine-5-oxide (X) in aqueous ammonium hydroxide solution was rapildy converted to the corresponding thiazolopyrimidine-2-carboxamide (XVIa). The structure of the thiazolopyrimidine was established by its independent synthesis and by its conversion to the simpler thiazolo[4,5-d]pyrimidine (XVII). A mechanism, involving the intermediate formation of a 4,1-azathionium ion (XXIV) has been proposed to explain these extremely facile rearrangements.

Recently a series of 1,3-disubstituted-5-halo-6-aminouracils has been described.[2] Since several members of this series exhibited significant biological activity as bronchodilators and antihypertensive agents, it became desirable to prepare a number of derivatives for further testing. Accordingly, five of the chlorouracils I were converted into the corresponding 6-amino-5-(carboxymethylthio)-uracils (II) by reaction with mercaptoacetic acid in alkaline solution. On treatment with acetic anhydride for several hours at 100°, the mercaptoacetic acids cyclized with loss of water to yield derivatives III of the hitherto unknown pyrimido[5,4-b][1,4]thiazine ring system.[3]

Tables I and II describe the compounds of types II and III, respectively, which have been prepared. The compounds of both series are stable, readily crystallizable solids. They are quite insoluble in water but dissolve in dilute sodium hydroxide solution from which they are reprecipitated upon acidification. The mercaptoacetic acids II could not be obtained when 5-bromo-6-aminouracils were used in place of the 5-chloro derivatives I. Instead, reductive debromination occurred, with formation of 6-aminouracils unsubstituted in position five.[4]

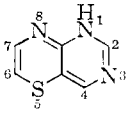
One representative pyrimido[5,4-b][1,4]thiazine, the 1-propyl-3-ethyl derivative IIIb, was selected for further chemical study because of the favorable effect of these particular alkyl groups on activity and toxicity of pyrimidines and purines tested as bronchodilators. It was found that the 5-oxide of this pyrimido[5,4-b]thiazine (IV) and the 5-oxide of one of its derivatives (X) were extremely labile compounds. The rearrangements of these sulfoxides and the proofs of structure of the compounds obtained from them are discussed in the following sections.

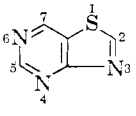
The Sulfoxide Rearrangement.—Oxidation of 1-propyl-3-ethyl-1*H*-pyrimido-[5,4-b][1,4]thiazine-2,4,7(3*H*,6*H*,8*H*)-trione (IIIb) in dry, alcohol-free chloroform with one equivalent of perbenzoic acid in benzene gave an excellent yield of a highly insoluble material which, after crystallization from butanone, gave good analytical values for the sulfoxide IV. The new compound was acidic as expected, but was unstable in aqueous suspension, giving rise to a highly colored purple product in a few hours even at room temperature. It was also quite insoluble in chloroform, benzene and ethyl acetate. It appeared very probable that the

(1) Present address: University of Minnesota, Minneapolis 14, Minn.

(2) E. F. Schroeder, U. S. Patents 2,731,465, Jan. 17, 1956, and 2,958,692, Nov. 1, 1960.

(3) The compounds in this paper are named as derivatives of 1H-pyrimido-[5,4-b][1,4]thiazine and thiazolo[4,5-d]pyrimidine. However, to aid in following the formulas, in all cases the pyrimidine ring





has been drawn on the left with the sulfur in the upper right. We are indebted to Dr. Leonard T. Capell of "Chemical Abstracts" for advice on nomenclature.

(4) V. Papesch and E. F. Schroeder, *J. Org. Chem.*, **16**, 1879 (1951). Similar reductive debrominations with mercaptans and thiamides have been detected previously; *e.g.*, see ref. 10.

TABLE I

5-(CARBOXYMETHYLTHIO)-6-AMINOURACILS (II)

Compound	R_1	R_2	M.p., °C.	Yield, %	Formula	Nitrogen, % Calcd.	Found
IIa	CH_3	CH_3	218–220	85	$C_8H_{11}N_3O_4S$	17.13	17.11
IIb	C_3H_7	C_2H_5	182–184	90	$C_{11}H_{17}N_3O_4S$	14.62	14.63
IIc	C_4H_9	C_4H_9	157–159	93	$C_{14}H_{23}N_3O_4S$	12.76	12.96
IId	CH_2=$CHCH_2$	C_2H_5	176–177	55	$C_{11}H_{15}N_3O_4S$	14.73	14.98
IIe	$HOCH_2CH_2$	C_2H_5	206–207	42[a]	$C_{10}H_{15}N_3O_5S$	14.53	14.77

[a] Melting point and yield after recrystallization from water.

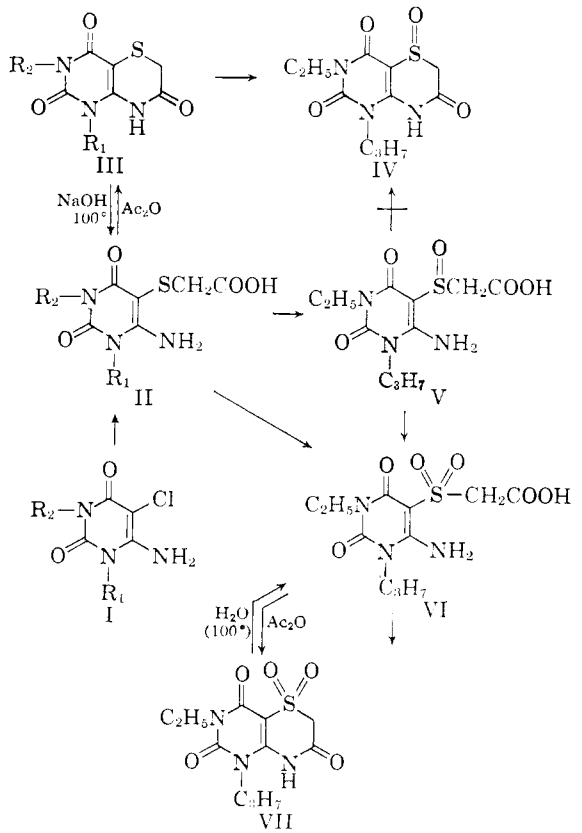
TABLE II

1*H*-PYRIMIDO[5,4-b][1,4]THIAZINE-2,4,7(3*H*,6*H*,8*H*)-TRIONES (III)

Compound[b]	R_1	R_2	M.p., °C.	Yield,[a] %	Formula	Nitrogen, % Calcd.	Found
IIIa	CH_3	CH_3	270–272	94	$C_8H_9N_3O_3S$	18.49	18.28
IIIb	C_3H_7	C_2H_5	186–188	87	$C_{11}H_{15}N_3O_3S$	15.60	15.42
IIIc	C_4H_9	C_4H_9	213–214	96	$C_{14}H_{21}N_3O_3S$	13.49	13.75
IIId	CH_2=$CHCH_2$	C_2H_5	231–233	92	$C_{11}H_{13}N_3O_3S$	15.72	15.98
IIIe	$HOCH_2CH_2$	C_2H_5	225–226	63	$C_{10}H_{13}N_3O_4S$	15.49	15.42

[a] Crude yield before recrystallization. [b] Variation in reaction conditions: IIIa, boil 5 minutes with acetic anhydride, then heat 1 hour at 100°; IIIe, see Experimental section.

compound IV was in fact the sulfoxide; its rather complex infrared spectrum provided some evidence for the presence of the sulfoxide group [9.46(w), 9.87(s), 9.99(s) μ].[5] No absorption in the 3 μ region, as would be expected from a hydroxyl group, was found.



For I, II and III

	R_1	R_2
a	CH_3	CH_3
b	C_3H_7	C_2H_5
c	C_4H_9	C_4H_9
d	CH_2=$CHCH_2$—	C_2H_5
e	$HOCH_2CH_2$—	C_2H_5

An alternate synthesis of the cyclic sulfoxide IV was attempted by way of the open-chain 1-propyl-3-ethyl-5-(carboxymethanesulfinyl)-6-aminouracil (V), obtained by oxidation in alkaline solution of the corresponding mercaptoacetic acid IIb. The open-chain sulfoxide V was also rather unstable, decomposing rapidly on boiling with water into sulfur dioxide and 1-propyl-3-ethyl-6-aminouracil. On attempted cyclization to IV with acetic anhydride, no identifiable compounds were obtained. The open-chain sulfoxide V could be oxidized to the corresponding sulfone, 1-propyl-3-ethyl-5-(carboxymethanesulfonyl)-6-aminouracil (VI) with peracetic acid. This sulfone, in contrast to the sulfoxide V, was a stable material and could be cyclized readily to VII. The cyclic sulfone VII, like the sulfoxide IV, was highly acidic. However, on heating with water at 100° it did not decompose but was hydrolyzed quantitatively to the open-chain sulfone VI. Attempts to oxidize the pyrimido[5,4-b][1,4]thiazine (IIIb) or the sulfoxide IV directly to the sulfone VII with excess oxidizing agent were unsuccessful. The insolubility and instability of the sulfoxide IV no doubt were responsible for this failure.

An attempt to crystallize the cyclic sulfoxide IV from abs. ethanol, resulted in the formation of a new, stable product VIIIa that was less acidic than the starting sulfoxide and much more soluble in chloroform, ethyl acetate or acetone. In a similar manner crystallization of the cyclic sulfoxide IV from methanol produced the corresponding 6-methoxypyrimido[5,4-b]thiazine (VIIIb), and crystallization from acetic acid yielded the 6-acetoxypyrimido[5,4-b]thiazine (VIIId).

The structures of these products were initially established by the conversion of the 6-ethoxypyrimido[5,4-b]thiazine (VIIIa) to 1-propyl-3-ethyl-6-aminouracil (XIV) and α-ethoxyacetamide (XV) as described in the next section of this paper. Advantage was also taken of the previous studies by Zahn[6] on the halogenation of 3-oxo-4*H*-benzo-

(5) See L. J. Bellamy, "The Infra-red Spectra of Complex Molecules," second edition, John Wiley and Sons, Inc., New York, N. Y., 1958, p. 359. The rearranged product VIIIc possessed a strong absorption band at 9.48 μ.

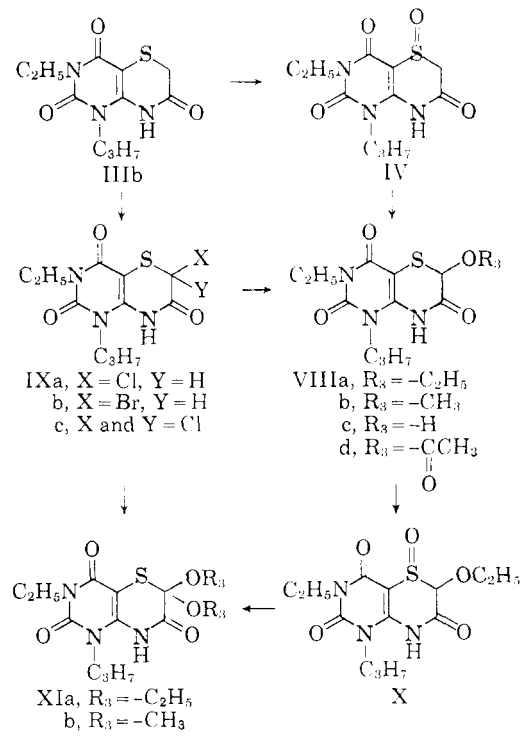
(6) K. Zahn, *Ber.*, **56**, 578 (1923).

1,4-thiazine and the alcoholysis of the halides so obtained. By the application of an analogous series of reactions to the pyrimido[5,4-b]thiazine (IIIb) the 6-chloro-, 6-bromo- and the 6,6-dichloropyrimido[5,4-b]thiazines (IXa, b and c) were obtained. Reaction of the 6-bromopyrimido[5,4-b]thiazine (IXb) with hot ethanol gave the same 6-ethoxypyrimido[5,4-b]thiazine (VIIIa) as had been obtained from the rearrangement of the sulfoxide IV. In a similar manner, the 6-bromopyrimido[5,4-b]thiazine (IXb) was converted to the 6-acetoxy derivative VIIId and the 6-chloropyrimido[5,4-b]thiazine (IXa) was converted to the corresponding 6-methoxy derivative VIIIb. The 6-acetoxypyrimido[5,4-b]thiazine VIIId was relatively unstable and decomposed slowly at room temperature over a period of several months. When heated in ethanol, it was easily changed to 6-ethoxypyrimido[5,4-b]thiazine (VIIIa).

Because of the instability of the sulfoxide IV in aqueous suspension and the purple color of the material that resulted, we were initially discouraged from investigating this decomposition. However, after the nature of this rearrangement had been clarified, we again examined the reaction of the sulfoxide IV with water. It was found that a suspension of the sulfoxide IV, m.p. 165–167°, in water was changed after two days at room temperature to the 6-hydroxypyrimido[5,4-b]thiazine (VIIIc), m.p. 205–207°. The latter compound exhibited a strong band at 3.03 μ (–OH) in its infrared spectrum, which was not present in the sulfoxide. There was also a marked difference in the acidity of an aqueous suspension of the sulfoxide IV (pH < 4, pH indicator paper) and of the 6-hydroxypyrimido[5,4-b]thiazine (VIIIc) (pH *ca.* 7). This same 6-hydroxy derivative VIIIc could be obtained by hydrolysis of the 6-acetoxypyrimido-[5,4-b]thiazine (VIIId) and could be converted to the 6-ethoxypyrimido[5,4-b]thiazine (VIIIa) by reaction with ethanol. In one instance, a sample of the crude sulfoxide IV rearranged spontaneously to the 6-hydroxy derivative VIIIc on several months storage in a closed bottle.

By further oxidation of the 6-ethoxypyrimido-[5,4-b]thiazine (VIIIa) with one equivalent of peracetic acid, the corresponding sulfoxide X was obtained. In contrast to the sulfoxide IV, the 6-ethoxysulfoxide X was stable in the presence of water and could be crystallized unchanged from ethanol. However, when the 6-ethoxysulfoxide X was heated with ethanol for four hours, rearrangement occurred and the corresponding 6,6-diethoxypyrimido[5,4-b]thiazine (XIa) was obtained. By analogy with the work of Zahn,[6] this same compound XIa was independently synthesized by the reaction of the 6,6-dichloropyrimido-[5,4-b]thiazine (IXc) with ethanol.

Further evidence for the existence of this rearrangement was obtained from the n.m.r. spectra of the 6-ethoxypyrimido[5,4-b]thiazine (VIIIa), the corresponding 6-ethoxysulfoxide X, and the 6,6-diethoxypyrimido[5,4-b]thiazine (XIa) prepared from it. The simpler cyclic sulfoxide IV was not sufficiently soluble in most solvents, nor sufficiently stable to permit a similar study to be made. For



both VIIIa and X, a strong singlet appeared in the n.m.r. spectra[7] at 5.04 and 5.12τ, respectively, clearly indicating the presence of a 6-H in both compounds. The 6,6-diethoxypyrimido[5,4-b]thiazine (XIa) obtained by the reaction of the 6-ethoxysulfoxide X with ethanol possessed no resonance band in this region, thus confirming the structures assigned above. (The region below 5.80τ in the spectrum of XIa was free of absorption with the exception of the small band at 2.73τ from the chloroform present in the deuteriochloroform.)

Reaction of Pyrimido[5,4-b]thiazines with Amines.—Treatment of the pyrimido[5,4-b]thiazine IIIb with ammonium hydroxide, methylamine or *n*-propylamine resulted in its conversion to the respective 6-amino-5-(carbamoylmethylthio)-uracil (XIIa, b or c). On gently heating these amides with one equivalent of aqueous sodium hydroxide, ammonia or amine was evolved and recyclization to the pyrimidothiazine occurred. This reaction was used to establish definitively the structure of the rearrangement product VIIIa obtained on treatment of the sulfoxide IV with ethanol.

The action of ammonium hydroxide on the 6-ethoxypyrimido[5,4-b]thiazine (VIIIa) resulted in an excellent yield of the 6-amino-5-(carbamoyl-ethoxymethylthio)-uracil (XIIIa). Since this could be recyclized back to the starting material VIIIa by heating with an equivalent quantity

(7) The nuclear magnetic resonance spectra of these compounds were run at 60 megacycles/sec. in deuteriochloroform using tetramethylsilane as an internal standard. We are indebted to Dr. Neal McNiven, Worcester Foundation for Experimental Biology, Shrewsbury, Mass., for determining these spectra for us.

P. Allen, P. J. Berner and E. R. Malinowski [*Chemistry & Industry*, 1164 (1961)] have recently reported the n.m.r. spectra of sulfides, sulfoxides and sulfones. Contrary to their report, the α-proton in our compound X (sulfoxide) absorbed at higher fields than the α-proton in VIIIa (sulfide). This probably indicates a variation with conformation in the effect of a sulfoxide on a α-hydrogen atom.

of aqueous sodium hydroxide, no rearrangement could have occurred during the reaction. Desulfurization of this 6-amino-5-(carbamoylethoxymethylthio)-uracil (XIIIa) with Raney nickel produced 1-propyl-3-ethyl-6-aminouracil (XIV) and α-ethoxyacetamide (XV), thus confirming the structural assignment of VIIIa. Because of the interconversions described in the previous section, this reaction also confirmed the structural assignments of VIIIb, c and d and IXa and b.

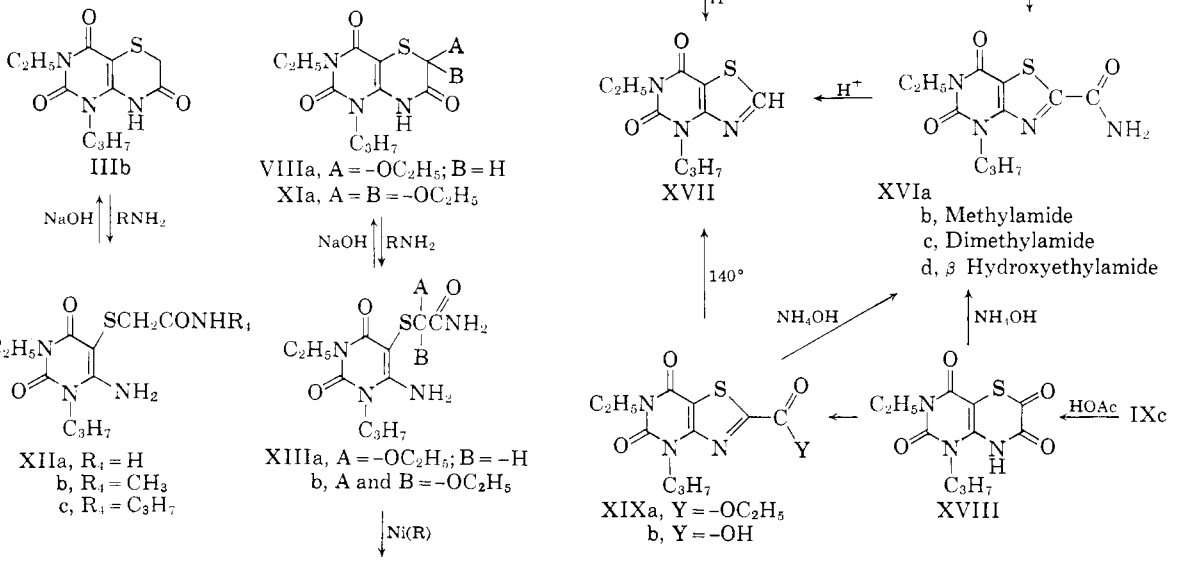
Since the possibility existed that the thiazine ring was opened by attack of the amine at position 8a rather than at the C-7 carbonyl, the 5-(carbamoylmethylthio)-uracil obtained from VIIIa by reaction with methylamine was also desulfurized with Raney nickel. The isolation of 1-propyl-3-ethyl-6-aminouracil (XIV) rather than the corresponding 6-methylaminouracil confirmed the structures depicted in the formulas.

The 6,6-diethoxypyrimido[5,4-b]thiazine (XIa) could also be cleaved to the corresponding 5-(carbamoyldiethoxymethylthio)-uracil (XIIIb). This latter compound, however, which is a monothioorthoester, decomposed when warmed with water to yield an, as yet unidentified, yellow compound, m.p. 257–258°.

Rearrangement of the Pyrimidothiazines to Thiazolo[4,5-d]pyrimidines.—While treatment of the pyrimidothiazine sulfoxide IV with aqueous ammonia or amines resulted only in colored decomposition products or black tars, which were not further investigated, similar treatment of the 6-ethoxysulfoxide X with ammonium hydroxide led to the formation of a new product XVIa of similar melting point, 186–188°, but differing greatly from the starting material in its ultraviolet (λ_{max} 337 mμ) and infrared spectra. The ultraviolet spectra were most useful in the classification of the various pyrimidines as to structural type (see Table III). Thus, all of the 5-substituted-6-aminouracils possessed maxima in the ultraviolet at or below 272 mμ with ϵ of 12,000 to 15,000. The pyrimidothiazines, on the other hand, possessed maxima from 295 to 333 mμ with ϵ of 6,000–8,750.[8] From this we concluded that the product from the reaction of the 2-ethoxysulfoxide X with ammonium hydroxide was not a simple carbamoylmethylthiouracil but probably still possessed a heterocyclic ring (thiazine or other) attached to the pyrimidine nucleus.

At first we considered a 6-iminopyrimido[5,4-b]-thiazine (analogous to XVIII) as a possible structure for XVIa, but after rereading the work of Zahn[6] on the rearrangement of 2,3-oxobenzothiazines to benzothiazoles, the formulation of the product of rearrangement as the thiazolopyrimidine XVIa seemed much more reasonable. Consequently, patterning our reactions of the pyrimido-[5,4-b]thiazines after those of Zahn,[6] we independently synthesized the thiazolo[4,5-d]pyrimidine (XVIa).

Solvolysis of the 6,6-dichloro-pyrimido[5,4-b]-thiazine IXc with glacial acetic acid gave a nearly quantitative yield of the pyrimidothiazine-2,4,6,7-tetraone (XVIII). The latter compound was converted to the ethyl thiazolo[4,5-d]pyrimidine-2-carboxylate (XIXa) by heating it under reflux in ethyl alcohol.

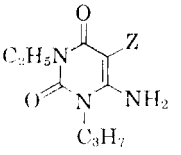


This ester XIXa on treatment with ammonium hydroxide in ethanol yielded the thiazolo[4,5-d]-pyrimidine-2-carboxamide (XVIa) identical in all

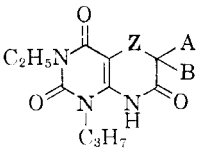
(8) Compound XVIII, with a maximum at 340 mμ, was an exception to the above statement. For the ultraviolet spectra of simple 1,4-thiazine-3-ones see G. de Stevens, A. Halamandaris and L. Dorfman, *J. Am. Chem. Soc.*, **80**, 5189 (1958).

TABLE III

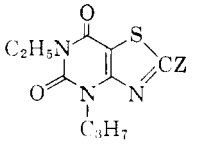
ULTRAVIOLET SPECTRA IN METHANOL



Compd.	Z	λ_{max}, mμ	ε × 10⁻³
IIb	S-CH_2COOH	272	14.7
V	$SOCH_2COOH$	269	15.0
VI	SO_2CH_2COOH	255	14.0
XIIa	SCH_2CONH_2	271	14.8
XIIIa	$SCH(OC_2H_5)CONH_2$	272	13.8
XIIIb	$SC(OC_2H_5)_2CONH_2$	272	13.3



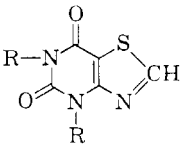
Compd.	Z	A	B	λ_{max}, mμ	ε × 10⁻³
IIIb	S	H	H	333	6.11
IV	SO	H	H	316	7.30
VII	SO_2	H	H	295	8.74
VIIIa	S	C_2H_5O-	H	325	8.21
X	SO	C_2H_5O-	H	310	6.39
				240	18.5
XIa	S	C_2H_5O-	C_2H_5O	318	7.08
				220	17.2
VIIIc	S	-OH	H	318	7.41
VIIId	S	CH_3COO-	H	317	7.79
				218	17.7



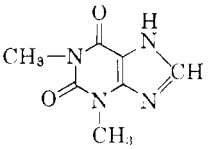
Cmpd.	Z	λ_{max}, mμ	ε × 10⁻³
XVII	H	301	5.98
XIXa	$-COOC_2H_5$	344	6.85
		227	21.2
XVIa	$-CONH_2$	337	6.15
		225	20.3

respects with that obtained from the rearrangement of the 6-ethoxysulfoxide X with ammonium hydroxide. This same thiazolopyrimidinecarboxamide XVIa was also obtained directly from the pyrimidothiazinetetraone XVIII by reaction with aqueous ammonia.

This investigation of the rearrangement of the pyrimidothiazines thus resulted in a new synthetic approach to the thiazolo[4,5-d]pyrimidines (the thiazolo[4,5-d]uracils) which until now have been difficult to prepare. Erlenmeyer and Furger[9] claimed to have obtained 4,6-dimethyl-5,7-dioxo-4,5,6,7-tetrahydrothiazolo[4,5-d]pyrimidine (XXb), a structural analog of theophylline (XXI), by the condensation of 1,3-dimethyl-5-bromobarbituric acid with thioformamide. However, later attempts by several investigators[10] to repeat this preparation were not successful. Childress and McKee[10a] succeeded in synthesizing the parent compound XXa by the action of potassium hypobromite on thiazole-4,5-dicarboxamide. Our attempts to methylate this compound XXa, thus leading to the 4,6-dimethyl derivative XXb, have not been successful.



XXa, R = H
b, R = CH_3



XXI

The sequence of reactions IIIb → IXc → XVIII → XIXb → XVII provides a very good method for the synthesis of thiazolo[4,5-d]pyrimidines. Thus, the pyrimidothiazine IIIb was converted to the pyrimidothiazinetetraone XVIII by chlorination with sulfuryl chloride and hydrolysis, in 84% yield. This, in turn, was readily transformed to the thiazolopyrimidine-2-carboxylic acid XIXb (83% yield) with aqueous alkali. Decarboxylation of XIXb occurred at 125–140° and gave a 97% yield of the 4-propyl-6-ethyl-5,7-dioxo-5,6,7,8-tetrahydrothiazolo[4,5-d]pyrimidine (XVII). Thus the over-all yield from the pyrimidothiazine IIIb to the thiazolopyrimidine XVII was 67.5%. The thiazolopyrimidine XVII was also obtained in good yield by the acid hydrolysis of either the 6,6-diethoxypyrimidothiazine (XIa) or the thiazolopyrimidine-2-carboxamide (XVIa).

Mechanism of the Rearrangement.—The rearrangements exemplified by the conversion of the sulfoxide IV to the 6-alkoxy derivatives VIIIa and b, the 6-acetoxy derivative VIIId and the 6-hydroxy derivative VIIIc and by the conversion of the 6-ethoxysulfoxide X to the 6,6-diethoxy derivative XIa and the thiazolopyrimidine XVIa, all involve a shift of a group (oxygen) on sulfur to the adjacent carbon atom. A similar rearrangement was originally discovered by Pummerer,[11] was probably run but not recognized by Zincke and Baeumer,[12] and was recently rediscovered by Horner and Kaiser[13a] and by Sorensen.[13b] The mechanism of this type of rearrangement has already been discussed in some detail.[13a,c] Here however, we must explain the extreme ease of rearrangement and the base catalysed rearrangement. A possible mechanism that will explain these two anomalies is depicted in the accompanying formulas. An acid or base catalysed proton shift would convert IV (or X) to XXII which could readily lose the elements of water (via XXIII) to form the neutral, resonance-stabilized 4,1-azathionium ion XXIV. The reaction of XXIV with the nucleo-

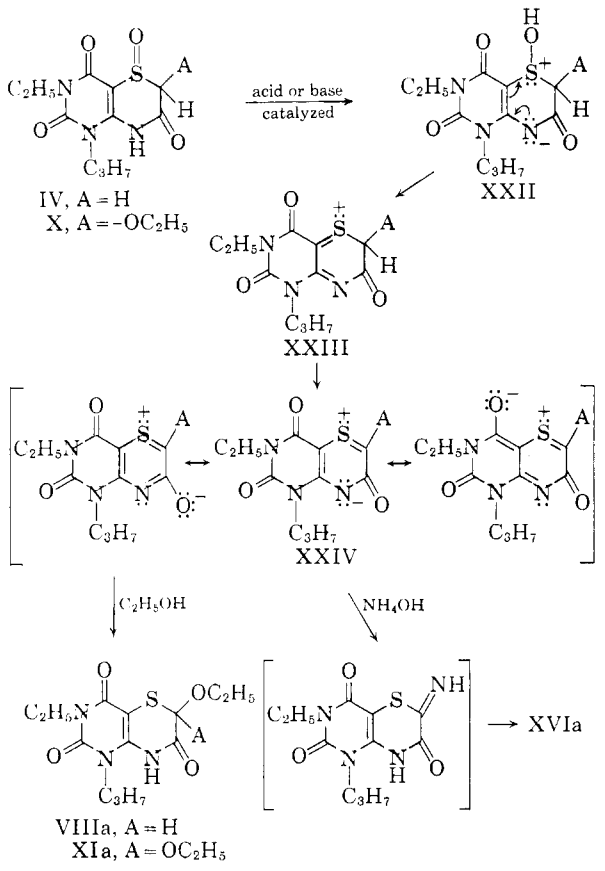
(9) H. Erlenmeyer and H. P. Furger, *Helv. Chim. Acta*, **26**, 366 (1943); **30**, 585 (1947).

(10) (a) S. J. Childress and R. L. McKee, *J. Am. Chem. Soc.*, **73**, 3862 (1951); (b) A. Maggiolo and G. H. Hitchings, *ibid.*, **73**, 4226 (1951); (c) G. P. Hager and C. Kaiser, *J. Am. Pharm. Assoc.*, **44**, 193 (1955); (d) H. P. Furger, *Helv. Chim. Acta*, **33**, 1689 (1950).

(11) R. Pummerer, *Ber.*, **43**, 1401 (1910).

(12) Th. Zincke and J. Baeumer, *Ann.*, **416**, 86 (1918).

(13) (a) L. Horner and P. Kaiser, *ibid.*, **626**, 19 (1959); (b) W. R. Sorensen, *J. Org. Chem.*, **24**, 978 (1959). Many of the rearrangements in this paper were run before these two papers appeared. (c) Compare also the chlorination of sulfides and the conversion of sulfoxides to α-chlorosulfides; F. G. Bordwell and B. M. Pitt, *J. Am. Chem. Soc.*, **77**, 572 (1955).



philic media should then lead to the final products, VIIIa, XIa, or XVIa.[14] Thus, the ease of formation and stability of the 4,1-azathionium ion can readily explain the facility of these rearrangements. If this mechanism is correct, many base-catalysed rearrangements of sulfoxides, as yet unexplored, should exist.

Experimental[15]

5-(Carboxymethylthio)-6-aminouracils.—A representative preparation in this series is that of the 1-propyl-3-ethyl derivative IIb. To a stirred suspension of 174 g. (0.75 mole) of 1-propyl-3-ethyl-5-chloro-6-aminouracil (Ib) in 660 ml. of 2.5 *N* sodium hydroxide (1.65 moles) was slowly added 95 g. of a commercial 80% aqueous solution of mercaptoacetic acid (0.82 mole). The mixture was heated to 90° for 0.5 hr. during which time solution occurred. On acidification of the cooled reaction mixture with 85 ml. of concd. hydrochloric acid a voluminous precipitate formed. This was separated by filtration, washed with water, and dried at 80° to yield 193 g. (90%) of the mercaptoacetic acid IIb, m.p. 178–180°. For analysis, a sample was dissolved in dil. sodium hydroxide, treated with charcoal, and filtered through Celite. On acidification, the pure 1-propyl-3-ethyl-5-(carboxymethylthio)-6-aminouracil (IIb) separated, m.p. 182–184°; λ_{max}^{KBr} 2.95, 3.02, 3.10, 3.38, 3.82, 5.78(m), 5.88(s), 6.10(s), 6.32(vs) and 13.10 μ.

1*H*-Pyrimido[5,4-*b*][1,4]thiazine-2,4,7(3*H*,6*H*,8*H*)-triones (IIIa-IIIe, Table II).—Typical in this series is the preparation of the 5-propyl-7-ethyl derivative IIIb. A mixture of 45.6 g. (0.16 mole) of the 5-(carboxymethylthio)-uracil IIb and 96 ml. of acetic anhydride (0.96 mole) was heated for 4 hours on a steam-bath in a flask attached to a short reflux condenser and protected by a calcium chloride tube. The hot, dark-colored solution was treated gradually with 50 ml. of water to decompose excess acetic anhydride, then diluted with 450 ml. more of water. The crystals, which formed when the solution was cooled, were separated by filtration, washed with water, and dried. The yield of crude, brownish material was 37.7 g. (87%). For purification, this was dissolved at room temperature in a slight excess of aqueous sodium hydroxide, decolorized with charcoal, and filtered through Celite. On acidification with acetic acid the almost colorless 1-propyl-3-ethyl-1*H*-pyrimido[5,4-b][1,4]thiazine-2,4,7(3*H*,6*H*,8*H*)-trione (IIIb) separated, m.p. 186–188°; λ_{max}^{KBr} 3.10, 3.16, 3.36, 5.91, 6.12, 6.22 and 13.16 μ. A sample recrystallized from ethanol melted at the same point.

In preparing the hydroxyethyl derivative IIIe a variation in isolation procedure was necessary because of the occurrence of acetylation of the hydroxyl group. After decomposition of the excess acetic anhydride the reaction mixture was evaporated to dryness under reduced pressure. The sirup remaining was covered with 5 parts of water containing about 2.2 equivalents of sodium hydroxide, heated for 15 minutes at 100°, then decolorized with charcoal. On acidification of the filtrate with acetic acid, the product IIIe separated.

1-Propyl-3-ethyl-1*H*-pyrimido[5,4-b][1,4]thiazine-2,4,7-(3*H*,6*H*,8*H*)-trione 5-Oxide (IV); "Sulfoxide" IV.—To an ice-cooled solution of 10.8 g. (0.04 mole) of the pyrimidothiazine IIIb in 120 ml. of dry, alcohol-free chloroform was added, during 0.5 hour, a solution of 5.52 g. of perbenzoic acid (0.04 mole) in 120 ml. of dry benzene. The temperature remained at 10–15° during the addition, and separation of a solid began. After being cooled for one additional hour, the crystals were separated by filtration, washed with a chloroform–benzene mixture, and dried. The yield of crude product IV was 10.8 g. (95%), m.p. 155–160° dec., darkening from 145°. This material was suitable for further synthetic work without purification. Crystallization presented some difficulty because of its low solubility in solvents such as chloroform, benzene and ethyl acetate, and its reactivity with alcohols and water. The most satisfactory solvent was 2-butanone. The crude product (2.0 g.) crystallized from 60 ml. of this solvent gave 1.0 g. of colorless IV, m.p. 165–167°, darkening from 162°; λ_{max}^{KBr} 3.34, 5.80, 6.04, 6.31, 9.87, 9.99 and 13.00 μ.

Anal. Calcd. for $C_{11}H_{15}N_3O_4S$: C, 46.31; H, 5.30; N, 14.73; S, 11.22. Found: C, 46.68; H, 5.53; N, 14.47; S, 11.13.

1-Propyl-3-ethyl-5-(carboxymethanesulfinyl)-6-aminouracil (V).—To an ice-cooled solution of 14.4 g. (0.05 mole) of the mercaptoacetic acid IIb and 7.00 g. (0.175 mole) of sodium hydroxide in 150 ml. of water was slowly added 8.1 ml. of a commercial peracetic acid solution (40%) in acetic acid (0.05 mole of peracid). The mixture was stirred for 0.5 hour longer, then acidified with 25 ml. of concd. hydrochloric acid. The crystals which formed were separated by filtration, washed with water, and dried in air to yield 12.0 g. (75%) of the monohydrate of V, m.p. 100–110° efferv.

Anal. Calcd. for $C_{11}H_{17}N_3O_5S \cdot H_2O$: N, 13.08; S, 9.98. Found: N, 12.91; S, 10.01.

The hydrate was suspended in 120 ml. of ethyl acetate and heated to boiling for 10 minutes. Solution occurred at first, followed by precipitation of the anhydrous V. The crystals were separated by filtration, washed with ethyl acetate and dried at 80° to yield 9.0 g. of V, m.p. 146–147° dec.; λ_{max}^{KBr} 2.94, 3.15, 3.35, 5.82, 6.04, 6.28, 9.73, 9.95 and 13.06 μ.

Anal. Calcd. for $C_{11}H_{17}N_3O_5S$: C, 43.55; H, 5.65; N, 13.85; S, 10.57. Found: C, 43.72; H, 5.34; N, 13.48; S, 10.73.

Compound V dissolved readily in hot water but began to decompose almost at once, sulfur dioxide being evolved (odor). 1-Propyl-3-ethyl-6-aminouracil (XIV) was isolated from the aqueous solution. In neutral aqueous solution the decomposition was greatly retarded. Attempts to ring-close V to the pyrimidothiazine-5-oxide (IV) by means of

(14) The mechanism proposed here differs from those previously discussed in that the oxygen on sulfur is completely separated from the molecule before the incoming group attacks the α-carbon atom. This may not be correct in the rearrangement that occurs in the solid state. See, *e.g.*, W. J. Kenney, J. A. Walsh and D. A. Davenport, *J. Am. Chem. Soc.*, **83**, 4019 (1961), and ref. 13c.

(15) We are indebted to Dr. R. T. Dillon and the Analytical Division of G. D. Searle and Co. for the analytical and optical data reported. All ultraviolet spectra were determined in methanol.

acetic anhydride yielded only dark tars, again indicating the instability of the compounds in question.

1-Propyl-3-ethyl-5-(carboxymethanesulfonyl)-6-aminouracil (VI).—To an ice-cooled solution of 14.4 g. (0.05 mole) of the mercaptoacetic acid IIb and 12 g. (0.3 mole) of sodium hydroxide in 180 ml. of water was slowly added 18 ml. of a commercial (40%) solution of peracetic acid in acetic acid (0.11 mole of peracid) at 10–15°. The reaction mixture was allowed to stand for 0.5 hour longer, then acidified with 25 ml. of concd. hydrochloric acid. The voluminous precipitate was separated by filtration, washed with cold water, and dried at 80°. The yield of crude VI was 12.2 g. (76%), m.p. 205–207° dec. For analysis a portion was dissolved in dil. sodium hydroxide, decolorized with charcoal, and filtered through Celite. On acidification of the filtrate with hydrochloric acid, colorless VI was obtained, m.p. 207–208° dec.; λ_{max}^{KBr} 2.91, 2.95, 3.01, 3.08, 3.35, 3.78, 5.82, 6.08, 6.25, 7.68–7.74, 8.91 and 12.99 μ.

Anal. Calcd. for $C_{11}H_{17}N_3O_6S$: C, 41.37; H, 5.37; N, 13.16; S, 10.04. Found: C, 41.51; H, 5.78; N, 13.32; S, 9.99.

The product was much more stable than the corresponding sulfinyl acetic acid V and could be recrystallized unchanged from 8 parts of hot water. Compound VI was also made in good yield by the peracetic acid oxidation of V in dil. sodium hydroxide solution. The product obtained melted at 205–207° and a mixed m.p. with authentic VI was not depressed.

1-Propyl-3-ethyl-1*H*-pyrimido[5,4-b][1,4]thiazine-2,4,7-(3*H*,6*H*,8*H*)-trione 5,5-Dioxide (VII).—A mixture of 9.5 g. of the sulfonylacetic acid VI and 19 ml. of acetic anhydride was heated for 4 hours at 100°. The dark solution was diluted with 120 ml. of abs. ethanol. On cooling, crystals precipitated which were separated by filtration, washed with ethanol and dried at 80° to yield 6.0 g. (67%) of the crude sulfone VII, m.p. 247–249°. Recrystallization of this material from 360 ml. of abs. ethanol gave 4.5 g. of product, m.p. 248–249°; λ_{max}^{KBr} 3.02, 3.34, 3.41, 5.73, 5.80, 6.01, 6.27, 7.63, 8.90 and 13.02 μ.

Anal. Calcd. for $C_{11}H_{15}N_3O_5S$: C, 43.84; H, 5.02; N, 13.95. Found: C, 44.23; H, 5.09; N, 14.12.

An aqueous suspension of the 5,5-dioxide VII had a strongly acidic reaction (pH < 4, pH indicator paper). On heating the suspension, solution occurred, accompanied by opening of the thiazine ring. Thus 1.0 g. of VII was heated for 5 minutes at 100° with 25 ml. of water. On cooling, a voluminous precipitate formed, which was separated by filtration, washed with water, and dried at 80°. The product, 0.70 g., m.p. 205–207° dec., was identified as the sulfonylacetic acid VI by m.m.p. and comparison of infrared spectra. An aqueous solution of the pyrimidothiazine-5,5-dioxide (VII), adjusted with sodium hydroxide to pH 7, was stable at room temperature. After 55 hours, unchanged VII was precipitated on acidification of the neutral solution with hydrochloric acid.

1-Propyl-3-ethyl-6-ethoxy-1*H*-pyrimido[5,4-b][1,4]-thiazine-2,4,7(3*H*,6*H*,8*H*)-trione (VIIIa). A. From the Sulfoxide IV.—Ten grams of the sulfoxide IV was dissolved in 150 ml. of abs. ethanol and boiled gently for 5 min. The solution was treated briefly with charcoal and filtered through Celite. On cooling, colorless crystals of product VIIIa separated, which were collected by filtration, washed with cold ethanol, and dried. The yield of crude material was 7.6 g., m.p. 163–165°. Concentration of the mother liquors yielded an additional 1.4 g. of product with a slightly lower melting point. The compound VIIIa was readily soluble in dil. sodium hydroxide, being reprecipitated unchanged upon acidification with acetic acid. In contrast to the starting sulfoxide IV, the product dissolved readily in chloroform and ethyl acetate, and was stable in the presence of water. For analysis, the crude product was recrystallized from 10 parts of ethanol to give VIIIa, m.p. 164–165°; λ_{max}^{KBr} 3.12, 3.18, 3.38, 5.84, 6.08, 6.20, 9.35, 9.48 and 13.23 μ.

Anal. Calcd. for $C_{13}H_{19}N_3O_4S$: C, 49.82; H, 6.11; N, 13.41; S, 10.23. Found: C, 49.86; H, 6.19; N, 13.55; S, 10.50.

B. From the 6-Bromopyrimidothiazine IXb.—The 6-bromopyrimidothiazine IXb (17.4 g.) was dissolved by heating with 150 ml. of abs. ethanol, gentle boiling being continued for 5 min. after solution was accomplished. The dark-colored, highly acidic solution was filtered to remove a few residual particals, then cooled for several hours. The separated crystals were collected on a filter, washed with cold ethanol and dried. The yield of crude product VIIIa was 14.2 g. (81%), m.p. 162–164°. Recrystallization from 10 parts of ethanol gave pure VIIIa, m.p. 164–165°.

C. From the 6-Acetoxypyrimidothiazine VIIId.—Sixty mg. of VIIId was dissolved in 1 ml. of abs. ethanol by warming, and held at 75° for 0.5 hr. After standing overnight at room temperature, a good yield (45 mg.) of product VIIIa separated, m.p. 163–165°.

D. From the 6-Hydroxypyrimidothiazine VIIIc.—A mixture of 1.0 g. of compound VIIIc, 15 ml. of abs. ethanol and 3 drops of concd. sulfuric acid was heated under reflux for 1 hr., complete solution having occurred in 40 min. On addition of 30 ml. of water crystallization began, and was allowed to proceed in the cold for 1 hr. The crystals were separated by filtration, washed with cold ethanol and dried to give 0.72 g. of VIIIa. Recrystallization from 5 ml. of abs. ethanol gave 0.54 g. of practially pure VIIIa, m.p. 163–164°.

The identity of the products obtained by methods B, C and D with product VIIIa of method A was established in each case by m.m.p. as well as by comparison of the infrared and ultraviolet spectra.

1-Propyl-3-ethyl-6-methoxy-1*H*-pyrimido[5,4-b][1,4]-thiazine-2,4,7(3*H*,6*H*,8*H*)-trione (VIIIb).—Five grams of the sulfoxide IV was dissolved in 60 ml. of warm methanol, the solution boiled for 5 min., then cooled in an ice-bath for 1 hour. The crystals that separated were collected by filtration, washed with cold methanol, and dried at 80° to yield 4.09 g. (76%) of VIIIb, m.p. 199–200° dec.; λ_{max} 323 mμ (ϵ 8140), 219 mμ (ϵ 16,200); λ_{max}^{KBr} 3.10, 3.17, 3.37, 5.87, 6.07, 6.18, 9.26, 9.43 and 13.18 μ.

Anal. Calcd. for $C_{12}H_{17}N_3O_4S$: C, 48.14; H, 5.73; N, 14.04. Found: C, 47.96; H, 5.50; N, 14.16.

The 6-methoxy compound VIIIb was also prepared in good yield by heating the 6-chloropyrimidothiazine IXa with methanol in a manner analogous to that used for the preparation of the corresponding 6-ethoxy compound VIIIa (method B).

1-Propyl-3-ethyl-6-bromo-1*H*-pyrimido[5,4-b][1,4]-thiazine-2,4,7(3*H*,6*H*,8*H*)-trione (IXb).—To a mixture of 13.45 g. (0.05 mole) of the pyrimidothiazine IIIb and 5 g. of sodium bicarbonate in 125 ml. of dry, alcohol-free chloroform was gradually added 8.0 g. of bromine in 50 ml. of the same solvent at 10–15°. The mixture was stirred for an additional 0.5 hr., then filtered to remove salts, and the filtrate evaporated almost to dryness on a steam-bath under a jet of air. The moist residue was covered with 50 ml. of hexane and again taken to dryness. The crude product IXb was obtained in practically quantitative yield (17.3 g.). For analysis a sample was crystallized from 20 parts of ethyl acetate giving light yellow crystals, m.p. 197–199° dec., λ_{max} 316 mμ (ϵ 7,760); λ_{max}^{KBr} 3.08, 3.14, 3.35, 5.90, 6.05 and 13.18 μ.

Anal. Calcd. for $C_{11}H_{14}BrN_3O_3S$: N, 12.07; Br, 22.95. Found: N, 11.95; Br, 22.71.

1-Propyl-3-ethyl-6-chloro-1*H*-pyrimido[5,4-b][1,4]-thiazine-2,4,7(3*H*,6*H*,8*H*)-trione (IXa).—To a suspension of 16.2 g. (0.06 mole) of the pyrimidothiazine IIIb in 90 ml. of glacial acetic acid, in a flask protected by a calcium chloride tube, was added 8.1 g. (0.06 mole) of sulfuryl chloride. Complete solution occurred almost immediately, the temperature rising rapidly to about 40°. Within a few minutes crystals began to separate, and hydrogen chloride was evolved. After 30 min. at room temperature, 90 ml. of hexane was added and the mixture cooled in ice. The crystals were separated by filtration, and washed first with hexane–acetic acid, then with hexane. After being dried at 80°, 16.4 g. (90%) of the monochloro derivative IXa was obtained as a tan-colored product, m.p. 202–205°, darkening from 190°. For analysis, this was crystallized from ethyl acetate–hexane to give colorless crystals, m.p. 203–205° dec., after darkening from 190°, λ_{max} 315 mμ (ϵ 8,350); λ_{max}^{KBr} 3.06, 3.33, 5.91, 6.08, 6.19 and 13.14 μ.

Anal. Calcd. for $C_{11}H_{14}ClN_3O_3S$: Cl, 11.67. Found: Cl, 11.66.

1-Propyl-3-ethyl-6-acetoxy-1*H*-pyrimido[5,4-b][1,4]-thiazine-2,4,7(3*H*,6*H*,8*H*)-trione (VIIId). A. From the Sulfoxide IV.—The sulfoxide IV (2.0 g.) was heated for 3 min. on a steam-bath with 8 ml. of glacial acetic acid. The light brown solution was diluted with 16 ml. of water and

cooled. The crystals that separated were collected on a filter, washed with water and dried giving 1.8 g. of crude product. This was purified by dissolving it in 4 parts of glacial acetic acid and diluting with 8 parts of water. Thus a nearly colorless product darkening at 148° and melting with effervescence at 159–160° was obtained; λ_{max}^{KBr} 2.92 (broad), 3.03, 3.36, 5.74, 5.90, 6.07, 6.18, 8.08, 8.27 and 13.15 μ. The acetoxy compound VIIId dissolved in 10 parts of hot ethyl acetate in contrast to the 50 parts required for the starting sulfoxide IV. An aqueous suspension of the former has a neutral reaction to *p*H indicator paper while the latter under the same conditions was strongly acidic (*p*H <4). The acetoxy compound VIIId was somewhat unstable; a sample kept in a dark bottle for 1 year changed into a red material.

Anal. Calcd. for $C_{13}H_{17}N_3O_5S$: C, 47.70; H, 5.24; N, 12.84; S, 9.79. Found: C, 47.68; H, 5.18; N, 12.45; S, 9.75.

B. From the 6-Bromopyrimidothiazine, IXb.—A mixture of the 6-bromothiazine IXb (348 mg., 0.001 mole), sodium acetate (82 mg., 0.001 mole) and glacial acetic acid (2 ml.) was heated for 2 min. in a steam bath. On dilution with water (4 ml.) and cooling, purple-colored crystals separated (300 mg.), which were purified by solution in 3 ml. of warm chloroform and addition of 4.5 ml. of hexane. On cooling, colorless crystals of the 2-acetoxy derivative VIIId separated in a yield of 150 mg., darkening from 148° and melting with effervescence at 158–159°. Identity with the product obtained by method A was established by m.m.p. as well as by comparison of infrared and ultraviolet spectra.

1-Propyl-3-ethyl-6-hydroxy-1*H*-pyrimido[5,4-b][1,4-thiazine-2,4,7(3*H*,6*H*,8*H*)-trione (VIIIc). A. By Spontaneous Rearrangement of the Sulfoxide IV.—A crude preparation of the sulfoxide IV, m.p. 155–160° (darkening from 145°), was stored in a dark, screw-capped glass bottle. When examined some eleven months later, the material had assumed a pink color and its melting point had risen to 178–181° (darkening from 170°). Also, its solubility in hot ethanol had decreased considerably, and the crystals separating on cooling were not the expected 6-ethoxypyrimidothiazine VIIIa but a product melting considerably higher (205–207° dec.). A 2-g. sample of the crude, pink material was then crystallized from 60 ml. of butanone to give 1.7 g. of the 6-hydroxypyrimidothiazine VIIIc, m.p. 205–207° dec.; λ_{max}^{KBr} 3.03–3.08(s), 3.35, 5.88, 6.10, 6.65, 7.64, 9.49 and 13.13 μ.

Anal. Calcd. for $C_{11}H_{15}N_3O_4S$: C, 46.31; H, 5.30; N, 14.73; S, 11.24. Found: C, 46.50; H, 5.43; N, 14.76; S, 11.51.

B. From the Sulfoxide IV in Aqueous Suspension.—One and one-half grams of IV, recrystallized from butanone and having m.p. 165–167°, was suspended in 25 ml. of water. The originally colorless and strongly acidic suspension began to turn pink within a few minutes. After having stood for 24 hours at room temperature, the solid phase had assumed a deep purple color and a small sample melted at about 200°, dec. The mixture was allowed to stand an additional 24 hours. The aqueous phase was then no longer acidic to *p*H indicator paper. The purple solid was separated by filtration, washed with water and dried, to give 1.25 g. of VIIIc, m.p. 198–200° dec. For purification, this was dissolved in 50 ml. of hot butanone, treated with decolorizing carbon, and filtered through Celite. To the filtrate was added 50 ml. of hexane. On being cooled, 1.05 g. of colorless product was obtained, m.p. 205–207° dec. Identity with the 6-hydroxypyrimidothiazine VIIIc prepared by method A was established by m.m.p. and comparison of infrared spectra.

C. From the 6-Acetoxypyrimidothiazine VIIId.—A suspension of 0.5 g. of VIIId in 5 ml. of water was heated on a steam-bath for 15 min. Solid phase was present throughout, but the supernatant liquid became acidic (*p*H *ca.* 4). The cooled mixture was filtered, and the solid washed with water and dried. The 0.40 g. of crude product, m.p. 202–204° dec., was purified as in B above and yielded 0.32 g. of VIIIc, m.p. 205–207° dec. (identity established by m.m.p. and infrared).

1-Propyl-3-ethyl-6-ethoxy-1*H*-pyrimido[5,4-b][1,4]-thiazine-2,4,7(3*H*,6*H*,8*H*)-trione 5-Oxide (X).—To a stirred suspension of 15.7 g. (0.05 mole) of the 6-ethoxypyrimidothiazine VIIIa in 60 ml. of glacial acetic acid was gradually added 10 ml. of a commercial 40% solution of peracetic acid in acetic acid (0.062 mole of peracid). The temperature was maintained at 30–40° by mild cooling during the addition. The homogeneous reaction mixture was kept for 0.5 hour at room temperature, then diluted with 200 ml. of water. The crystals which precipitated on cooling were separated by filtration, washed with water, and dried. The yield of crude 5-oxide X was 13.7 g., m.p. 185–186°. Recrystallization of this product from ethanol (275 ml.) gave 10.3 g. of the 6-ethoxy-5-oxide X, m.p. 186–187°; λ_{max}^{KBr} 3.19 (broad), 3.36, 5.73(m), 5.84(s), 6.01(s), 6.30, 9.12, 9.78 and 12.97 μ.

Anal. Calcd. for $C_{13}H_{19}N_3O_5S$: C, 47.40; H, 5.81; N, 12.76; S, 9.73. Found: C, 47.33; H, 5.87; N, 12.38; S, 9.91.

1-Propyl-3-ethyl-6,6-diethoxy-1*H*-pyrimido[5,4-b][1,4]-thiazine-2,4,7(3*H*,6*H*,8*H*)-trione (XIa). A. From the 6-Ethoxysulfoxide X.—A suspension of X (10 g.) in 100 ml. of abs. ethanol was heated under reflux for 4 hours, complete solution occurring in 0.5 hour. The red solution was concentrated to about 40 ml. under reduced pressure, then diluted with 20 ml. of water. On cooling for 2 hours, crystals formed which were separated by filtration, washed with 50% aqueous ethanol and dried to give 6.4 g. (60%) of XIa. Recrystallization from 25 ml. of ethanol gave 5.2 g. of product, m.p. 165–167°; λ_{max}^{KBr} 3.12, 3.31, 5.73, 5.81, 6.09, 6.18 and 13.09 μ. A m.m.p. with the monoethoxy compound VIIIa, which melts at about the same point, was sharply depressed.

Anal. Calcd. for $C_{15}H_{23}N_3O_5S$: C, 50.40; H, 6.49; N, 11.76; S, 8.97. Found: C, 50.58; H, 6.42; N, 11.58; S, 9.10.

B. From the 6,6-Dichloropyrimidothiazine IXc.—One gram of IXc was mixed with 5 ml. of abs. ethanol. Complete solution occurred almost at once, the temperature rose to 40°, and a red color developed. After standing for 0.5 hour at 25°, the now strongly acidic solution was heated just to boiling, then diluted with 5 ml. of water. On cooling the solution, crystals formed. These were separated by filtration, washed with 50% aqueous ethanol, and dried to give 0.80 g. (76%) of the colorless diethoxy derivative XIa, m.p. 164–166°, identical in all respects (m.m.p. and infrared spectrum) with that prepared by method A. The product XIa dissolved in an equivalent of aqueous alkali and was reprecipitated unchanged upon acidification with acetic acid.

1-Propyl-3-ethyl-6,6-dimethoxy-1*H*-pyrimido[5,4-b][1,4]-thiazine-2,4,7-(3*H*,6*H*,8*H*)-trione (XIb).—The 6,6-dichloropyrimidothiazine IXc (6.76 g., 0.02 mole) was mixed with methanol (35 ml.). Almost immediate solution occurred, the temperature rose to 40°, and hydrogen chloride was evolved. On standing at room temperature for 0.5 hr., crystals appeared. The deep red mixture was cooled in ice for several hours, filtered, and the crystals washed with aqueous methanol (50%). After being dried, 5.05 g. (76%) of colorless product XIb was obtained, m.p. 162–163°; λ_{max} 319 mμ (ϵ 7,020), 219 mμ (ϵ 16,200); λ_{max}^{KBr} 3.12, 3.33, 5.83, 6.03, 6.18 and 13.19 μ.

Anal. Calcd. for $C_{13}H_{19}N_3O_5S$: C, 47.40; H, 5.81; N, 12.76. Found: C, 47.41; H, 5.87; N, 12.72.

1-Propyl-3-ethyl-6,6-dichloro-1*H*-pyrimido[5,4-b][1,4]-thiazine-2,4,7(3*H*,6*H*,8*H*)-trione (IXc).—In a flask fitted with a reflux condenser and protected by a calcium chloride drying tube, were placed 26.9 g. (0.1 mole) of the pyrimidothiazine IIIb, 250 ml. of dry carbon tetrachloride and 27 g. (0.2 mole) of sulfuryl chloride. The mixture was heated under reflux for 1.5 hr., then filtered, while hot, to remove a small amount of undissolved material. By adding 50 ml. of hexane to the filtrate and cooling in an ice-bath for 1 hour, one obtained colorless crystals of product IXc. These were separated by filtration and washed first with a carbon tetrachloride–hexane mixture, then with hexane. After being dried in air for 0.5 hr., the crystals were placed in a desiccator and kept under reduced pressure until completely dry. During this time a slight yellowing occurred. The yield was 20.5 g. (61%), m.p. 145–7° dec., after darkening from 125°, λ_{max} 316 mμ (ϵ 6,900); λ_{max}^{KBr} 3.14, 3.33, 5.82, 6.12, 6.57, 6.72 and 13.12 μ. No suitable solvent for recrystallization was found.

Anal. Calcd. for $C_{11}H_{13}Cl_2N_3O_3S$: N, 12.42; Cl, 20.97. Found: N, 11.85; Cl, 20.80.

1-Propyl-3-ethyl-5-(carbamoylmethylthio)-6-aminouracil (XIIa).—A solution of 2.0 g. of the pyrimidothiazine IIIb in 6 ml. of concd. ammonium hydroxide was kept at room temperature for 6 days. The crystals which formed were separated by filtration, washed with water and dried to give 2.08 g. (97%) of the amide XIIa, m.p. 202–204°. Crystallization from 30 ml. of ethanol, or 50 ml. of hot water, gave pure material, m.p. 204–206°; λ_{max}^{KBr} 2.95, 3.11, 3.34, 5.86, 6.08, 6.27 and 13.02 μ.

Anal. Calcd. for $C_{11}H_{18}N_4O_3S$: C, 46.14; H, 6.34; S, 11.20. Found: C, 46.53; H, 6.22; S, 11.23.

1-Propyl-3-ethyl-5-(N-methylcarbamoylmethylthio)-6-aminouracil (XIIb), m.p. 185–187°, was prepared in 87% yield by the reaction of the pyrimidothiazine IIIb with aqueous methylamine (25%) as described above.

Anal. Calcd. for $C_{12}H_{20}N_4O_3S$: C, 47.99; H, 6.71; S, 10.66. Found: C, 48.25; H, 6.77; S, 10.60.

1-Propyl-3-ethyl-5-(N-propylcarbamoylmethylthio)-6-aminouracil monohydrate (XIIc), m.p. 102–103° efferv., was prepared in 87% yield by the reaction of IIIb with aqueous *n*-propylamine.

Anal. Calcd. for $C_{14}H_{24}N_4O_3S \cdot H_2O$: C, 48.53; H, 7.56; S, 9.25. Found: C, 48.79; H, 7.30; S, 9.01.

The monohydrate was dehydrated by dissolving 1.20 g. in 20 ml. of ethyl acetate, boiling for 5 min., diluting with 15 ml. of hexane, and cooling. Anhydrous crystals of XIIc were obtained in a yield of 0.90 g., m.p. 158–159°.

Anal. Calcd. for $C_{14}H_{24}N_4O_3S$: C, 51.24; H, 7.37; N, 17.06. Found: C, 51.74; H, 7.21; N, 17.28.

1-Propyl-3-ethyl-5-(carbamoylmethanesulfonyl)-6-aminouracil, m.p. 236–238°, was prepared in 74% yield by the reaction of the pyrimidothiazine-5,5-dioxide VII with concd. ammonium hydroxide.

Anal. Calcd. for $C_{11}H_{18}N_4O_5S$: N, 17.60. Found: N, 17.27.

A sample of this material heated at 100° for 0.5 hr. in dilute aqueous sodium hydroxide liberated ammonia. On acidification with hydrochloric acid, the sulfonylacetic acid VI, m.p. 207–208°, was precipitated.

1-Propyl-3-ethyl-5-(N-methylcarbamoylmethanesulfonyl)-6-aminouracil, m.p. 197–199°, was prepared from VII (72% yield) using methylamine as described above.

Anal. Calcd. for $C_{12}H_{20}N_4O_5S$: N, 16.86; S, 9.65. Found: N, 16.85; S, 9.55.

1-Propyl-3-ethyl-5-(carbamoylethoxymethylthio)-6-aminouracil (XIIIa).—A solution of 4.40 g. of the 6-ethoxypyrimidothiazine (VIIIa) in 15 ml. of concd. ammonium hydroxide was allowed to stand at room temperature for 3 days. The crystals which had formed were separated by filtration, washed with water and dried to give 3.55 g. (77%) of XIIIa, m.p. 221–223°. Crystallization from 265 ml. of ethanol gave pure XIIIa, m.p. 222–223° dec. The compound was soluble in approximately 300 parts of hot water.

Anal. Calcd. for $C_{13}H_{22}N_4O_4S$: C, 47.26; H, 6.71; N, 16.96; S, 9.70. Found: C, 47.47; H, 6.83; N, 16.76; S, 9.71.

The filtrate from the crude amide XIIIa, on acidification with acetic acid, gave 0.80 g. of starting compound VIIIa, m.p. 163–165°, which indicated that the ammonolysis had not gone to completion.

Under mild conditions, the amide XIIIa can be recyclized to the 6-ethoxypyrimidothiazine VIIIa. A suspension of 330 mg. (0.001 mole) of the former in 10 ml. of water containing 0.0015 mole of sodium hydroxide was heated for 1 hour at 100°. Ammonia was evolved and solution occurred. Upon acidification with dil. acetic acid, VIIIa precipitated (160 mg., m.p. and m.m.p. 163–165°).

1-Propyl-3-ethyl-5-(N-methylcarbamoylethoxymethylthio)-6-aminouracil, m.p. 164–166°, was prepared from the 6-ethoxypyrimidothiazine (VIIIa) in 98% yield by the use of methylamine as described above.

Anal. Calcd. for $C_{14}H_{24}N_4O_4S$: C, 48.82; H, 7.02; N, 16.27. Found: C, 49.02; H, 6.95; N, 16.36.

1-Propyl-3-ethyl-5-(carbamoyldiethoxymethylthio)-6-aminouracil (XIIIb).—A solution of 3.80 g. of the 6,6-diethoxypyrimidothiazine (XIa) in 20 ml. of concd. ammonium hydroxide was held at room temperature, with occasional shaking, for 13 days. A voluminous precipitate, which separated shortly after the solution was first prepared, was identified as the ammonium salt of the starting compound XIa. This was gradually replaced, during the incubation, by a more granular precipitate. The latter was separated by filtration, washed with water and dried to give 2.10 g. of colorless product XIIIb, m.p. 188–189° efferv., after crystallization from ethanol; λ_{max}^{KBr} 2.94, 3.06–3.10, 3.33, 5.86, 5.92, 6.10, 6.49, 8.94, 10.37 and 13.02 μ.

Anal. Calcd. for $C_{15}H_{28}N_4O_5S$: C, 48.11; H, 7.00; N, 14.96; S, 8.56. Found: C, 48.04; H, 7.09; N, 14.96; S, 8.59.

A suspension of the amide XIIIb in water underwent extensive decomposition when heated on a steam-bath for 2 hr. A bright yellow, unidentified product, m.p. 257–258°, was obtained.

Proof of Structures VIIIa and XIIIa.—In a 1-l. flask fitted with a sealed stirrer and reflux condenser were placed 3.00 g. of the amide XIIIa, 200 ml. of abs. ethanol and 30 g. of Raney nickel (stored under water and washed several times by decantation with ethanol before use). The mixture was heated under reflux for 3 hr., then filtered through Celite. The filtrate was evaporated to dryness under reduced pressure and the sirupy residue taken up in 5 ml. of water. On cooling, crystals separated which were identified as the monohydrate of 1-propyl-3-ethyl-6-aminouracil (XIV). The yield was 1.60 g. (82%). Dehydration by stirring for 1 hr. with 50 ml. of anhydrous ether gave the anhydrous product, m.p. 170–172°. A mixture with authentic XIV[4] showed no depression in m.p.

The aqueous filtrate from the monohydrate was extracted several times with 5-ml. portions of ether. The aqueous phase, on evaporation to dryness, gave a solid. This on crystallization from benzene yielded 200 mg. of ethoxyacetamide[16] (XV), m.p. 79–81°. Identity was established in the usual manner (m.m.p. and infrared spectra).

Treatment of 3.15 g. of 1-propyl-3-ethyl-5-(N-methylcarbamoylethoxymethylthio)-6-aminouracil with Raney nickel in ethanol as described for the amide XIIIa gave a reaction mixture from which was isolated 1.50 g. (77%) of the monohydrate of XIV. This located the methyl group on the amide function rather than on the 6-amino group.

6-Ethyl-4,5,6,7-tetrahydro-5,7-dioxo-4-propylthiazolo[4,5-d]pyrimidine-2-carboxamide (XVIa). A. From the 6-Ethoxysulfoxide X.—Ten grams of X was mixed with 30 ml. of concd. ammonium hydroxide. Complete solution occurred almost at once; the temperature rose rapidly to 40–45°; and within a few minutes a new precipitate began to form. After having stood overnight, the mixture was diluted with 20 ml. of water, cooled in ice, and filtered. The crystals were washed with water and dried, giving 7.60 g. (89%) of product XVIa, m.p. 186–188°. A 2.0-g. sample was crystallized from 20 ml. of ethanol for analysis; m.p. 186–188°. A m.m.p. with starting compound X was depressed by 20°.

Anal. Calcd. for $C_{11}H_{14}N_4O_5S$: C, 46.80; H, 5.00; N, 19.84; S, 11.36. Found: C, 47.01; H, 5.00; N, 19.95; S, 11.41.

B. From the Pyrimidothiazine-tetraone XVIII.—One gram of compound XVIII was mixed with 5 ml. of concd. ammonium hydroxide. Complete solution occurred almost immediately, the temperature rising to 40°. Within a few minutes a new precipitate began to form. The mixture was kept at room temperature for 2.5 hr., then cooled in ice and filtered. The crystals were washed with water and dried to give 0.85 g. (85%) of XVIa, m.p. 185–187°.

C. From the Ethyl Thiazolopyrimidine-2-carboxylate (XIXa).—To a solution of 0.5 g. of XIXa in 5 ml. of ethanol was added 5 ml. of concd. ammonium hydroxide. After having stood at room temperature for 0.5 hr., the mixture was heated to a gentle boil for 10 min., diluted with 5 ml. of water and cooled for several hours. The crystals were separated by filtration, washed with water and dried to give 0.40 g. (89%) of XVIa, m.p. 186–188°.

The identity of the products prepared by methods B and C with compound XVIa of method A was established by m.m.p. and by comparison of their infrared spectra.

6-Ethyl-4,5,6,7-tetrahydro-5,7-dioxo-4-propylthiazolo[4,5-d]pyrimidine-2-N-methylcarboxamide (XVIb), m.p. 180–181°, was prepared from the pyrimido-thiazine-

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tetraone XVIII in 65% yield by the use of aqueous methylamine (see B above).

Anal. Calcd. for $C_{12}H_{16}N_4O_3S$: C, 48.63; H, 5.44; N, 18.91. Found: C, 48.80; H, 5.30; N, 18.68.

6-Ethyl-4,5,6,7-tetrahydro-5,7-dioxo-4-propylthiazolo[4,5-d]pyrimidine-2-N,N-dimethylcarboxamide (XVIc), m.p. 111–112°, was prepared using aqueous dimethylamine from the pyrimidothiazine-tetraone XVIII by method B above (52% yield) and from the ester XIXa by method C (86% yield).

Anal. Calcd. for $C_{13}H_{18}N_4O_3S$: C, 50.31; H, 5.85; S, 10.32. Found: C, 49.96; H, 6.16; S, 10.59.

6-Ethyl-4,5,6,7-tetrahydro-5,7-dioxo-4-propylthiazolo[4,5-d]pyrimidine-2-N-(β-hydroxyethyl)-carboxamide (XVId), m.p. 125–127°, was prepared from XVIII and 2-aminoethanol by method B above.

Anal. Calcd. for $C_{13}H_{18}N_4O_4S$: C, 47.84; H, 5.56; S, 9.82. Found: C, 47.98; H, 5.62; S, 10.15.

1-Propyl-3-ethyl-1*H*-pyrimido[5,4-b][1,4]thiazine-2,4,6,7-(3*H*,8*H*)-tetraone (XVIII).—A mixture of 10 g. of the 6,6-dichloropyrimidothiazine (IXc) and 30 ml. of glacial acetic acid was heated for 20 min. on a steam-bath. Complete solution occurred and hydrogen chloride evolved. The solution was diluted with 30 ml. of hexane and cooled. Bright yellow crystals of product XVIII formed. These were separated by filtration, washed with hexane, and dried to give 8.20 g. (98%) of XVIII, m.p. 236–238°; λ_{max} 340 mμ (ε 6,060), 227 mμ (ε 19,400); λ_{max}^{KBr} 3.04, 3.10, 3.33, 5.80, 6.05, 6.48 and 13.18 μ.

Anal. Calcd. for $C_{11}H_{13}N_3O_4S$: C, 46.63; H, 4.62; N, 14.83; S, 11.32. Found: C, 46.40; H, 4.59; N, 14.81; S, 11.60.

For preparative purposes, the isolation of the 6,6-dichloro intermediate IXc may be omitted. In a 500-ml. flask provided with a reflux condenser and dropping funnel were placed 26.9 g. of the pyrimidothiazine IIIb (0.1 mole) and 135 ml. of glacial acetic acid. At room temperature, during about 15 min., 29.7 g. (0.22 mole) of sulfuryl chloride was added. Complete solution of the solid phase occurred after about half of the chlorinating agent had been added. Then a new precipitate formed, probably the monochloro derivative of IIIb, but this redissolved as the addition of sulfuryl chloride was completed. The yellow solution was heated for 40 min. on a steam-bath, with concomitant evolution of hydrogen chloride. To the now deep red solution was added 150 ml. of hexane. On cooling, bright yellow crystals of the tetraone XVIII precipitated. These were separated by filtration, washed with hexane and dried to yield 23.7 g. (84%) of XVIII, m.p. 235–237°.

Ethyl 6-Ethyl-4,5,6,7-tetrahydro-5,7-dioxo-4-propylthiazolo[4,5-d]pyrimidine-2-carboxylate (XIXa).—A suspension of 2.4 g. of the pyrimidothiazine-tetraone XVIII in 20 ml. of abs. ethanol was heated under reflux for 1 hour; complete solution occurred after 0.5 hr. The solution was diluted with 15 ml. of water and cooled. The colorless crystals were separated by filtration, washed with cold 50% aqueous ethanol and dried in air. The yield of ethyl ester XIXa was 2.10 g. (80%), m.p. 81–82°; λ_{max}^{KBr} 3.33, 5.67, 5.81, 5.92, 6.34, 7.92, 9.25, 9.46, 9.85 and 13.12 μ. Concentration of the filtrate gave an additional 0.40 g., m.p. 79–81°. Recrystallization of the first crop material from aqueous ethanol failed to change the m.p.

Anal. Calcd. for $C_{13}H_{17}N_3O_4S$: C, 50.14; H, 5.51; N, 13.50. Found: C, 50.18; H, 5.87; N, 13.33.

6-Ethyl-4,5,6,7-tetrahydro-5,7-dioxo-4-propylthiazolo[4,5-d]pyrimidine-2-carboxylic Acid (XIXb). A. By Hydrolysis of the Ethyl Ester XIXa.—A mixture of 0.94 g. (0.003 mole) of the ester XIXa and 10 ml. of 0.5 *N* sodium hydroxide (0.005 mole) was shaken for a few minutes at room temperature until complete solution occurred. The temperature rose spontaneously to 35°. After having stood for 0.5 hr. longer, the solution was acidified with 2.5 *N* hydrochloric acid. An oil separated which rapidly solidified. The crystals were separated by filtration, washed with cold water and dried in air to give 0.74 g. of the monohydrate of the acid XIXb, m.p. 102–104° with strong effervescence.

Anal. Calcd. for $C_{11}H_{13}N_3O_4S \cdot H_2O$: N, 13.94; S, 10.64. Found: N, 13.82; S, 10.58.

Drying the monohydrate for 3 hr. at 80° gave colorless anhydrous acid XIXb, m.p. 130–132° efferv.; λ_{max} 334 mμ (ε 5,670), 225 mμ (ε 20,100); λ_{max}^{KBr} 2.82–2.91, 3.36, 5.82, 5.99–6.08, 6.39, 6.68, 8.03 and 13.13 μ.

Anal. Calcd. for $C_{11}H_{13}N_3O_4S$: N, 14.83; S, 11.32. Found: N, 14.83; S, 11.06.

B. By Rearrangement of the Pyrimidothiazine-tetraone XVIII.—Compound XVIII (9.6 g., 0.033 mole) was dissolved in 100 ml. of 1 *N* sodium hydroxide (0.1 mole). After having stood at room temperature for 0.5 hr., the yellow solution was slowly acidified with 10 ml. of concd. hydrochloric acid. An oil separated which rapidly solidified. After being cooled, the crystals were separated by filtration, washed with cold water and dried first in air, then for 3 hr. at 80°. The yield of anhydrous acid XIXb was 8.00 g. (83%), m.p. 130–132° efferv. Identity with the product of method A was established by m.m.p. (no depression) and by comparison of infrared spectra.

6-Ethyl-4,5,6,7-tetrahydro-5,7-dioxo-4-propylthiazolo[4,5-d]pyrimidine (XVII).—Four and one-half grams (0.016 mole) of the thiazolopyrimidine-2-carboxylic acid (XIXb) was placed in a flask inserted in an oil-bath and gradually heated to 135–140°. Rapid evolution of carbon dioxide began at about 125°. Heating was continued for 0.5 hr. On being cooled, the sirupy reaction product solidified to give 3.7 g. (97%) of the crude thiazolopyrimidine XVII, m.p. 77–79°. After crystallization from aqueous ethanol, the 3.00 g. of pure product melted at 78–79°; λ_{max}^{KBr} 3.20, 3.35, 5.82, 6.00, 6.35, 6.69 and 13.18 μ.

Anal. Calcd. for $C_{10}H_{13}N_3O_2S$: C, 50.19; H, 5.48; N, 17.56; S, 13.40. Found: C, 50.04; H, 5.51; N, 17.16; S, 13.42.

The same compound was also obtained in good yield by the acid hydrolysis of either the 6,6-diethoxypyrimidothiazine (XIa) or the thiazolopyrimidine-2-carboxamide (XVIa). Two grams of either compound was dissolved in a mixture of 20 ml. of acetic acid, 5 ml. of water and 1 ml. of concd. sulfuric acid. After being heated for 10 hr. on a steam-bath, the reaction mixture was evaporated to a sirup. On being cooled and diluted with water, the thiazolopyrimidine XVII crystallized, m.p. 77–79°. Infrared spectra were identical with that of XVII made from the carboxylic acid XIXb.