Ring Opening of Dihydro-1,4-oxathiins

MAURICE ARMAND CORBEIL, MICHAEL CURCUMELLI-RODOSTAMO, ROBERT JAMES FANNING, BRUCE ALLAN GRAHAM, MARSHALL KULKA, AND JAMES BENJAMIN PIERCE

Uniroyal Limited, Research Laboratories, Guelph, Ontario

Received December 8, 1972

Acid hydrolysis of 5,6-dihydro-2-methyl-1,4-oxathiin-3-carboxanilide gives 2-(2-hydroxyethylthio)-acetoacetanilide enol. 3-Carbonyl-substituted 5,6-dihydro-1,4-oxathiins were found to undergo ring cleavage by nucleophilic nitrogen attack on C-2. Thus the following reactions were observed: 3-acetyl-5,6-dihydro-2-methyl-1,4-oxathiin on treatment with hydrazine gives 4-(2-hydroxyethylthio)-3,5-dimethylpyrazole, instead of the hydrazone. The 1,4-oxathiins, *N*-(5,6-dihydro-2-methyl-1,4-oxathiin-3-ylcarbonyl)-*N'*-phenylurea and 5,6-dihydro-2-methyl-1,4-oxathiin-3-carboxylic acid hydrazide rearrange to give 5-(2-hydroxyethylthio)-6-methyl-1-phenyluracil and 4-(2-hydroxyethylthio)-3-methyl-2-pyrazolin-5-one, respectively. Finally, treatment of 5,6-dihydro-2-methyl-1,4-oxathiin-3-carbonyl chloride with 2-aminopyridine and with 2-aminopyrimidine affords 4*H*-3-(2-hydroxyethylthio)-2-methylpyrido[1,2-*a*]pyrimidin-4-one and 4*H*-3-(2-hydroxyethylthio)-2-methylpyrimido[1,2-*a*]pyrimidin-4-one, respectively, as the predominant products.

L'hydrolyse acide du dihydro-5,6 méthyl-2 oxathiine-1,4 carboxanilide-3 a produit l'énol (hydroxy-2 éthylthio)-2 acétoacétanilide. Les composés dihydro-5,6 oxathiine-1,4 carboxyl-3 substitués ont subi un clivage du cycle consécutivement à l'attaque de la position C-2 par un azote nucléophile. Par suite, les réactions suivantes furent observées: l'acétyl-3 dihydro-5,6 méthyl-2 oxathiine-1,4 a produit lors d'une réaction avec l'hydrazine l'(hydroxy-2 éthylthio)-4 diméthyl-3,5 pyrazole au lieu de l'hydrazone. Les oxathiines-1,4 *N*-(dihydro-5,6 méthyl-2 oxathiine-1,4 carbonyl-3) *N'*-phénylurée et l'hydrazide de l'acide dihydro-5,6 méthyl-2 oxathiine-1,4 carboxylique-3 ont produit par réarrangement l'(hydroxy-2 éthylthio)-5 méthyl-6 phényl-1 uracile et l'(hydroxy-2 éthylthio)-4 méthyl-3 pyrazoline-2 one-5, respectivement. Finalement, la réaction du chlorure de dihydro-5,6 méthyl-2 oxathiine-1,4 carbonyle-3 avec l'amino-2 pyridine et avec l'amino-2 pyrimidine à conduit, comme produits principaux, à l'(hydroxy-2 éthylthio)-3-4*H* méthyl-2 pyridopyrimidine[1,2-*a*]one-4 et à l'(hydroxy-2 éthylthio-3-4*H* méthyl-2 pyrimido pyrimidine[1,2-*a*]one-4 respectivement. [Traduit par le journal]

Can. J. Chem., 51, 2650 (1973)

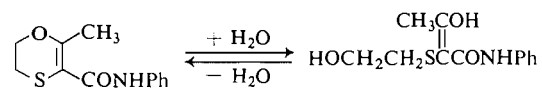
The discovery that 5,6-dihydro-1,4-oxathiins and more particularly 5,6-dihydro-2-methyl-1,4-oxathiin-3-carboxanilide (Vitavax®)[1] (**1**) and its sulfone (Plantvax®) possess systemic fungicidal properties (1) has stimulated interest in 1,4-oxathiin chemistry and has given impetus to the search for other systemic fungicides.

The purpose of this paper is to discuss the ring opening of several 3-carbonyl-substituted 5,6-dihydro-1,4-oxathiins by nucleophilic attack on C-2.

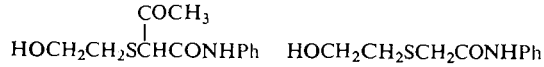
Recently Wilson demonstrated that 5,6-dihydro-2-methyl-1,4-oxathiin undergoes acid-catalyzed hydrolytic cleavage to form (2-hydroxyethylthio)-2-propanone (2). It has been found in this laboratory that 5,6-dihydro-2-methyl-1,4-oxathiin-3-carboxanilide (**1**) undergoes similar hydrolytic cleavage with formation of the enol form **2** of 2-(2-hydroxyethylthio)acetoacetanilide (**3**) (eq. 1). This compound was also prepared from 2-mercaptoethanol and 2-chloroacetoacetanilide.

That the hydrolysis product is the enol **2** and not the keto form **3** has been demonstrated by the purple color it gives in alcoholic ferric chloride, by its rapid dissolution in aqueous sodium and ammonium hydroxide, and by its i.r. and n.m.r. spectra. The ketone carbonyl band is absent in the i.r. spectrum and the singlet at 15.5 p.p.m. in the n.m.r. spectrum is indicative of an enolic proton. The enolization appears to be aided by the sulfur atom since unsubstituted β-ketoamides are largely ketonic. Similar enolization has been observed in 2-thio-1,3-diketones (3).

The cleavage product **2** was converted readily to **1** by heating in benzene with azeotropic water



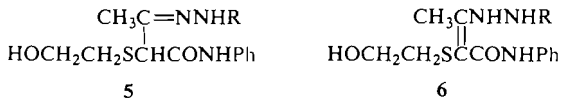
[1] **1** **2**



3 **4**

[1]®Uniroyal's registered trademark.

removal in the presence of an acid catalyst. As expected, it is sensitive to base, and in aqueous sodium hydroxide undergoes deacetylation to furnish 2-(2-hydroxyethylthio)acetanilide (**4**). Similar deacetylations have been previously observed (4–6). **2** forms a 2,4-dinitrophenylhydrazone (**5**) which is also obtained by treatment of the oxathiin **1** with 2,4-dinitrophenylhydrazine reagent. The n.m.r. spectrum of the hydrazone shows a singlet at 4.67 p.p.m. which is not affected on treatment of the sample with deuterium oxide. Assignment of this singlet to a proton at C-2 shows the hydrazone to have the imine structure **5**, rather than the alternative enamine structure **6**.

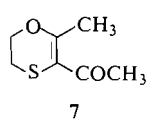


5 **6**

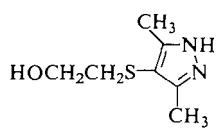
R = 2,4-dinitrophenyl

Mattsson and Bertilsson have shown that 5,6-dihydro-2-methyl-1,4-oxathiin-3-carboxanilide (**1**) can also be cleaved by amines (7). Thus a solution of **1** and pentylamine on standing at room temperature for several days affords 2-(2-hydroxyethylthio)-3-pentylaminocrotonanilide. A number of reactions of 3-carbonyl-substituted 5,6-dihydro-1,4-oxathiins involving nucleophilic attack on C-2 by nitrogen have been encountered in this laboratory.

One such reaction constitutes an example of the known conversion of β-alkoxy-α,β-unsaturated ketones to pyrazoles on treatment with hydrazine (8). Thus from 3-acetyl-5,6-dihydro-2-methyl-1,4-oxathiin (**7**) and hydrazine a product was obtained which was identified as 4-(2-hydroxyethylthio)-3,5-dimethylpyrazole (**8**). The n.m.r. spectrum (DMSO-d_6) of this product (**8**) shows a singlet at 2.23 p.p.m. attributed to two equivalent methyl groups and two triplets at 2.56 and 3.45 p.p.m. characteristic of the two methylenes of a 2-hydroxyethylthio group.

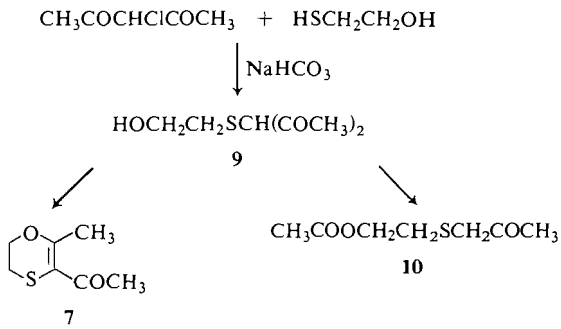


7

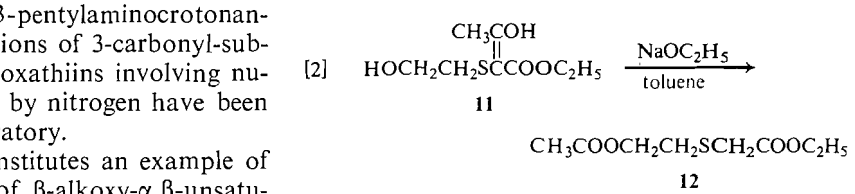


8

The preparation of the oxathiin **7** now warrants brief consideration. Reaction of 3-chloro-2,4-pentanedione with 2-mercaptoethanol in the presence of sodium bicarbonate gave a neutral and an acidic compound (Scheme 1). The acidic compound, presumably **9**, was converted to the desired oxathiin **7** by acid-catalyzed dehydration. The neutral product was identified as **10** by comparison of its i.r. and n.m.r. spectra with those of an authentic sample prepared by acetylation of (2-hydroxyethylthio)-2-propanone (2). It probably formed by rearrangement of **9**. A similar rearrangement, observed in this laboratory, consists in the conversion of ethyl 2-(2-hydroxyethylthio) acetoacetate (**11**) to ethyl (2-acetoxyethylthio)acetate (**12**) in the presence of sodium ethylate (eq. 2).



SCHEME 1



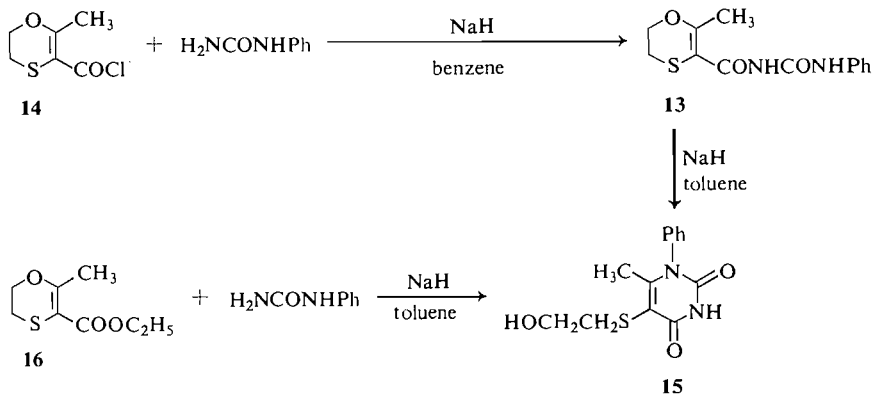
11

$CH_3COOCH_2CH_2SCH_2COOC_2H_5$

12

The identity of compound **12** was established by comparison of its i.r. and n.m.r. spectra with those of the compound obtained by acetylation of ethyl (2-hydroxyethylthio)acetate (9).

Another reaction involving nucleophilic attack by nitrogen on C-2 of a 1,4-oxathiin gave a 2-hydroxyethylthio-substituted uracil. Thus *N*-(5,6-dihydro-2-methyl-1,4-oxathiin-3-ylcarbonyl)-*N'*-phenylurea (**13**), prepared from 5,6-dihydro-2-methyl-1,4-oxathiin-3-carbonyl chloride (**14**) and *N*-phenylurea, when heated in refluxing toluene in the presence of sodium hydride rearranged to 5-(2-hydroxyethylthio)-6-methyl-1-phenyluracil (**15**) in 57% yield (Scheme 2). Compound **15** was also obtained in an attempt to make **13** by the method of Wolfe and Trimitsis (10). Thus treatment of ethyl 5,6-dihydro-2-methyl-1,4-oxathiin-3-carboxylate (**16**) (*1b*) with *N*-phenylurea and sodium hydride in toluene at reflux temperature gave **15** in 55% yield. Since, as shown above, compound **13** rearranges to



14 13 16 15

SCHEME 2

15 in a suspension of sodium hydride in refluxing toluene, it is probably an intermediate in the reaction of the ester **16** with *N*-phenylurea to form **15**. The i.r. and n.m.r. spectra of the rearrangement product **15** are in agreement with the proposed structure. The solubility of the product in aqueous sodium hydroxide and the fact that the *N*-methyl derivative can easily be prepared by the method of Senda and Suzui (11) provided further evidence for the uracil structure **15**. Confirmation of the presence of the alcoholic function came from the conversion of **15** to a chloride on treatment with thionyl chloride in chloroform. 1-(5-Chloro-2-methylphenyl)-5-(2-hydroxyethylthio)-6-methyluracil was obtained from ethyl 5,6-dihydro-2-methyl-1,4-oxathiin-3-carboxylate **16** and *N*-(5-chloro-2-methylphenyl)-urea in the same manner as was **15**.

A further example of ring opening of a dihydro-1,4-oxathiin by intramolecular nitrogen attack was encountered when an *n*-butanol solution of 5,6-dihydro-2-methyl-1,4-oxathiin-3-carboxylic acid hydrazide (**17**) was heated at reflux to give the rearranged isomer 4-(2-hydroxyethylthio)-3-methyl-2-pyrazolin-5-one (**18**) (eq. 3). The n.m.r. spectrum of **18** shows the two methylene triplets characteristic of a 2-hydroxyethylthio group. The solubility of **18** in aqueous sodium carbonate and its u.v. absorption at 242 nm are in accord with the assigned 2-pyrazolin-5-one structure. A strong band in the i.r. spectrum (KBr) between 2400 and 2900 cm^{-1}, ascribed by De Stevens and co-workers (12) to the pyrazolinone zwitterion, shows the important contribution of the tautomeric form **19**.

Cleavage of the dihydro-1,4-oxathiin ring was also demonstrated in the reaction of the acid chloride **14** with 2-aminopyridine in benzene in

[3]

17 18 19

the presence of triethylamine. This reaction gave the amide **20** in only 4% yield. The major reaction product **21**, isolated in 56% yield, was identified as 4*H*-3-(2-hydroxyethylthio)-2-methylpyrido[1,2-*a*]pyrimidin-4-one (**21***a*), an isomer of **20**.

The i.r. spectrum of compound **21** revealed the presence of a hydroxyl group. The n.m.r.

20

21*a* 21*b*

22 23

a R = H
b R = CH_3

spectrum shows two triplets (J = 6Hz), centered at 3.67 and 2.98 p.p.m., instead of the methylene multiplets present in the spectra of dihydro-1,4-oxathiins. The foregoing data indicated that cleavage of the dihydro-1,4-oxathiin ring had occurred resulting in the formation of a 2-hydroxyethylthio group. At this stage, structures **21***a* and **21***b* were considered for compound **21**.

The problem of distinguishing between a 2- and a 4-pyrido[1,2-*a*]pyrimidinone is not new and has been the subject of several investigations (13–19). In particular, it has been shown by Adams and Pachter (15) and by Allen *et al.* (19) that the u.v. spectra of 2- and 4-pyrido[1,2-*a*]-pyrimidinones are characteristically different in the relative values of the extinction coefficients of the maxima occurring in the regions of 240–270 nm (region *a*) and 300–400 nm (region *b*). Typically the 4-ones show a ratio of extinction coefficients $\varepsilon_b/\varepsilon_a$ greater than 1 whereas for 2-ones this ratio is less than $\frac{1}{3}$. Table 1 lists the u.v. data for compounds **22***a* and **23** (19) together with those we found for compound **21**. Comparison of the extinction-coefficient ratios ($\varepsilon_b/\varepsilon_a$) clearly indicates that **21** has the 4-one structure **21***a* rather than the alternative 2-one structure **21***b*.

Structure **21***a* received further spectroscopic support. The n.m.r. spectrum of compound **21** shows a single-proton doublet (8.93 p.p.m.) downfield from the bulk of aromatic absorption by 0.9 p.p.m. In structure **21***a* the low-field position of this doublet can be attributed to the deshielding of the 6-proton by the keto group whereas a similar effect is not possible in structure **21***b*. A comparable deshielding was found by Mendel for the 6-proton of compound **22***b* (20).

Confirmation of structure **21***a* rests on chemical evidence. Formation of the alternative structure **21***b* would be expected to involve the intermediacy of the minor reaction product **20**.

TABLE 1. Comparison of u.v. data of 2- and 4-pyrido[1,2-*a*]pyrimidinones*

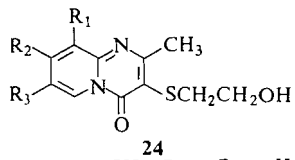
Compound	λ_a	ε_a	λ_b	ε_b	$\varepsilon_b/\varepsilon_a$
21*a*	248	11.5	352	14.3	1.24
22*a*†	248	10.0	348	10.0	1.00
	258	9.6			
23†	268	10.0	324	3.2	0.31

*The wavelength is given in nm and the extinction coefficient is expressed as $\varepsilon \times 10^{-3}$.
†U.v. data from ref. 19.

The latter, however, was shown not to be a reaction intermediate, since it was recovered quantitatively after being subjected to the reaction conditions.

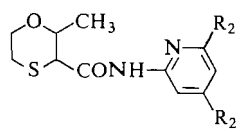
Reaction of the acid chloride **14** with 2-amino-3-, -4-, and -5-methylpyridine furnished the 4-pyrido[1,2-*a*]pyrimidinones **24***a*, **24***b*, and **24***c*, respectively. The dihydro-1,4-oxathiin carboxamides were shown by n.m.r. spectroscopy to form in low yield.

However, reaction of compound **14** with 2-amino-6-methylpyridine and with 2-amino-4,6-dimethylpyridine led exclusively to the amides **25***a* and **25***b*. Clearly, the 6-methyl group hinders attack of the electrophile on the ring nitrogen. Failure of the ring nitrogen of 2-amino-6-methylpyridine to participate in reactions with bifunctional electrophiles has been well documented (13, 21–23).



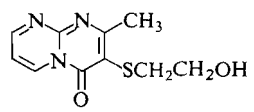
24

a $R_1 = CH_3$, $R_2 = R_3 = H$
b $R_1 = R_3 = H$, $R_2 = CH_3$
c $R_1 = R_2 = H$, $R_3 = CH_3$

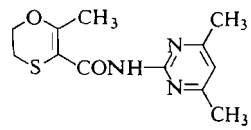


25

a $R_1 = CH_3$, $R_2 = H$
b $R_1 = R_2 = CH_3$



26



27

Treatment of the acid chloride **14** with 2-aminopyrimidine furnished the 4-pyrimido[1,2-*a*]pyrimidinone **26**. The structural assignment follows from the presence in the n.m.r. spectrum of a low-field absorption (centered at 9.2 p.p.m.) due to the C-6 and -8 protons (see above) and from analogy with the behavior of the 2-aminopyridines. As expected, reaction of compound **14** with 2-amino-4,6-dimethylpyrimidine yielded only the amide **27**.

Experimental

I.r. spectra were obtained on Perkin-Elmer 237B or 521 grating i.r. spectrometers. The n.m.r. spectra were recorded using an R-20 Hitachi Perkin-Elmer spectrometer and are expressed in p.p.m. (δ values) relative to tetramethylsilane as standard. Melting points were determined on a Gallenkamp melting point apparatus and are

uncorrected. Ultraviolet spectra were measured on a Perkin-Elmer 402 spectrometer and the analyses were performed on a Perkin-Elmer 240 elemental analyzer.

2-(2-Hydroxyethylthio)acetoacetanilide Enol (2)

To a solution of 2-chloroacetoacetanilide (53 g, 0.25 mol) in methanol (50 ml) and pyridine (25 g) was added 2-mercaptoethanol (20 g, 0.26 mol) and the solution stirred for 15 min with occasional cooling on a water bath maintaining the temperature at 35 to 40°. The reaction mixture was allowed to stand at room temperature for 2 h and then poured into water (200 ml). The material obtained by solidification of the precipitated oil was collected, washed well with cold water, and dried. Crystallization from toluene gave large white crystals (54.6 g or 87.5%) of m.p. 64–66°. Recrystallization from toluene yielded a pure product melting at 66–67°. N.m.r. ($CDCl_3$): 15.5 (1H, s, OH), 9.33 (1H, s, NH), 7.33 (5H, m, aromatic), 3.67 (2H, m, CH_2O), 2.63 (2H, t, CH_2S), 2.63 (1H, t, OH), 2.33 (3H, s, CH_3); i.r. ($CHCl_3$): 3680, 3620, 3325 cm^{-1}.

Anal. Calcd. for $C_{12}H_{15}NO_3S$: C, 56.89; H, 5.96; N, 5.52. Found: C, 56.80; H, 6.20; N, 5.61.

The enol **2** was converted in 65% yield to 2-(2-chloroethylthio)acetoacetanilide enol by treatment with thionyl chloride in benzene at room temperature, m.p. 83–85°.

Anal. Calcd. for $C_{12}H_{14}ClNO_2S$: C, 53.03; H, 5.19; N, 5.15; Cl, 13.04; S, 11.8. Found: C, 53.05; H, 5.61; N, 5.66; Cl, 12.8; S, 11.8.

Ring Opening of 5,6-Dihydro-2-methyl-1,4-oxathiin-3-carboxanilide with Aqueous Acid

A mixture of 5,6-dihydro-2-methyl-1,4-oxathiin-3-carboxanilide (23.5 g, 0.10 mol), 10% aqueous hydrochloric acid (100 ml), and toluene (200 ml) was heated to 80° while stirred rapidly. The mixture was maintained at this temperature for 1 h, allowed to cool, and the aqueous and organic layers were then separated. The toluene phase was extracted with cold 10% aqueous sodium hydroxide (2 × 100 ml) and the aqueous extract acidified with dilute hydrochloric acid. The product immediately oiled out of the acidic solution. It was extracted with toluene (2 × 100 ml) and the toluene phase was reduced in volume (to about 75 ml) by distillation under reduced pressure. The product was crystallized from the remaining toluene by cooling to −20° and scratching to induce crystallization. Thus was obtained 2-(2-hydroxyethylthio)acetoacetanilide (14.5 g or 57%) of m.p. 63–67°. The i.r. spectrum of this material proved to be identical to that of the material isolated from reaction of 2-chloroacetoacetanilide with mercaptoethanol.

5,6-Dihydro-2-methyl-1,4-oxathiin-3-carboxanilide (1)

To a solution of 2-(2-hydroxyethylthio)acetoacetanilide enol (**2**) (23.5 g, 0.09 mol) in benzene (65 ml) was added *p*-toluenesulfonic acid (0.1 g) and the reaction mixture was heated under reflux for 2 h with azeotropic water removal in a Dean–Stark trap. The solution was diluted with benzene (100 ml) and then washed with cold 5% aqueous sodium hydroxide and with water. The solvent was distilled off *in vacuo* and the residue crystallized from toluene to yield white crystals (19.9 g or 90%) of m.p. 93–95°. N.m.r. ($CDCl_3$): 9.33 (1H, s, NH), 7.5 (5H, m, aromatic), 4.80 (2H, m, CH_2O), 3.52 (2H, m, CH_2S), 2.36 (3H, s, CH_3).

Anal. Calcd. for $C_{12}H_{13}NO_2S$: C, 61.28; H, 5.53; N, 5.96. Found: C, 61.29; H, 5.58; N, 5.87.

Deacetylation of 2-(2-Hydroxyethylthio)acetoacetanilide (2) to 2-(2-Hydroxyethylthio)acetanilide (4)

To a solution of 2-(2-hydroxyethylthio)acetoacetanilide (25 g, 0.1 mol) in benzene (100 ml) was added 10% aqueous sodium hydroxide (100 ml) and the reaction mixture stirred at 35 to 40° for 1.5 h. The reaction mixture was cooled and the precipitate collected, washed with water, and dried. The white solid thus obtained (15.5 g or 70%) melted at 80–81° and did not depress the m.p. of an authentic sample of 2-(2-hydroxyethylthio)acetanilide prepared from 2-mercaptoethanol and chloroacetanilide. The i.r. spectrum was identical with that of the authentic sample.

The treatment of 2-(2-hydroxyethylthio)acetanilide with thionyl chloride in chloroform yielded 2-(2-chloroethylthio)acetanilide in 65% yield, m.p. 91–93°.

Anal. Calcd. for $C_{10}H_{12}ClNOS$: C, 52.27; H, 5.26; N, 6.09. Found: C, 52.10; H, 5.20; N, 5.93.

2,4-Dinitrophenylhydrazone (5) of 2-(2-Hydroxyethylthio)acetoacetanilide (2)

To a solution of 5,6-dihydro-2-methyl-1,4-oxathiin-3-carboxanilide (10.5 g, 0.045 mol) in methanol (250 ml) was added a solution of 2,4-dinitrophenylhydrazine (9 g, 0.045 mol) in concentrated sulfuric acid (100 ml), water (400 ml), and methanol (100 ml). After allowing the reaction mixture to stand at room temperature for 2 days, the orange crystals were filtered, washed with water and with methanol, and dried. The yellow solid (18 g or 90%) melted at 188–190° and at 191–193° after recrystallization from acetonitrile. N.m.r. (DMSO-d_6): 10.86 (1H, s, NH), 10.31 (1H, s, NH), 6.8–8.9 (8H, m, aromatic), 4.9 (1H, t, J = 5.5 Hz, OH), 3.4–3.8 (2H, m, CH_2O), 2.72 (2H, t, J = 6.5 Hz, CH_2S), 2.29 (3H, s, CH_3); i.r. (KBr): 3240, 3310, 3590 cm^{-1}.

Anal. Calcd. for $C_{18}H_{19}N_5O_6S$: C, 49.87; H, 4.41. Found: C, 50.26; H, 4.52.

The same compound was obtained when 2-(2-hydroxyethylthio)acetoacetanilide (**2**) was treated similarly with 2,4-dinitrophenylhydrazine.

3-Acetyl-5,6-dihydro-2-methyl-1,4-oxathiin (7)

Sodium bicarbonate (92.4 g, 1.1 mol) was added to a stirred mixture of 3-chloro-2,4-pentanedione (24)(134.5 g, 1 mol), benzene (400 ml), 2-mercaptoethanol (78.1 g, 1 mol), and water (200 ml). After 0.5 h the organic layer was separated and extracted with 2 *N* sodium hydroxide (500 ml). The organic layer was washed with water (200 ml) and concentrated *in vacuo* to yield *(2-acetoxyethylthio)-2-propanone* (**10**) (5.9 g or 3.4%), a colorless liquid of b.p. 100° at 0.4 mm. N.m.r. ($CDCl_3$): 4.16 (2H, t, J = 6.5 Hz, CH_2O), 3.33 (2H, s, CH_2CO), 2.72 (2H, t, J = 6.5 Hz, CH_2S), 2.26 (3H, s, CH_3CO), 2.04 (3H, s, acetoxy); i.r. (film): 1730 (ester CO), 1700 cm^{-1} (ketone CO).

Anal. Calcd. for $C_7H_{12}O_3S$: C, 47.70; H, 6.86. Found: C, 47.52; H, 6.76.

The aqueous sodium hydroxide extract from above was acidified with hydrochloric acid and extracted with benzene (2 × 250 ml). The organic extracts were combined, added to *p*-toluenesulfonic acid (5 g), and heated to reflux with azeotropic removal of the water formed in the

reaction. When no further water was liberated the reaction mixture was cooled and washed successively with 1 *N* sodium hydroxide (200 ml) and water (200 ml). The organic layer was concentrated *in vacuo* to a syrup which was distilled through a vigreux column to give 3-acetyl-5,6-dihydro-2-methyl-1,4-oxathiin (**7**) (43 g or 27%), a yellow liquid of b.p. 89–90° at 0.5 mm. N.m.r. ($CDCl_3$): 4.31 (2H, m, CH_2O), 2.96 (2H, m, CH_2S), 2.26, 2.23 (each 3H, s, CH_3); i.r. (film): 1670 (CO), 1635 cm^{-1} (C=C).

Anal. Calcd. for $C_7H_{10}O_2S$: C, 53.13; H, 6.37. Found: C, 52.79; H, 6.45.

*Rearrangement of Ethyl 2-(2-hydroxyethylthio)acetoacetate (**11**) to form Ethyl (2-acetoxyethylthio)-acetate (**12**)*

A sample of ethyl 2-(2-hydroxyethylthio)acetoacetate was prepared by the method given in ref. 1*b* and was not isolated. Thus to ethyl 2-chloroacetoacetate (25) (15.0 g, 0.089 mol) and 2-mercaptoethanol (6.8 g, 0.089 mol) in a mixture of toluene (200 ml) and water (50 ml) was added sodium bicarbonate (7.5 g, 0.089 mol). The reaction mixture was stirred for 18 h, the phases were separated, and some toluene (100 ml) distilled from the toluene phase to remove any residual water. To the resulting toluene solution of ethyl 2-(2-hydroxyethylthio)acetoacetate was added 6 drops of a 10% solution of sodium ethoxide in absolute ethanol. The mixture was heated on a steam bath for 2 h and the toluene was then removed under reduced pressure. The residue was distilled to give ethyl (2-acetoxyethylthio)acetate (10.2 g or 56%), b.p. 96–100° at 0.4 mm. This material proved to be identical in every respect to a sample made by acetylation of ethyl (2-hydroxyethylthio)acetate (9). N.m.r. ($CDCl_3$): 4.24 (2H, t, J = 6.5 Hz, OCH_2CH_2), 4.19 (2H, quartet, J = 7.2 Hz, OCH_2CH_3), 3.28 (2H, s, SCH_2CO), 2.86 (2H, t, J = 6.5 Hz, SCH_2CH_2), 2.05 (3H, s, CH_3CO), 1.27 (3H, t, J = 7.2 Hz, CH_3CH_2); i.r. (film): 1635, 1225, 1025 cm^{-1}.

*Reaction of 3-Acetyl-5,6-dihydro-2-methyl-1,4-oxathiin (**7**) with Hydrazine to form 4-(2-Hydroxyethylthio)-3,5-dimethylpyrazole (**8**)*

To a stirred solution of 3-acetyl-5,6-dihydro-2-methyl-1,4-oxathiin (3.16 g, 0.02 mol) in isopropanol (5 ml), cooled in an ice-water bath, was added dropwise a solution of aqueous hydrazine hydrate (85%, 1.3 g, 0.022 mol) in isopropanol (5 ml). After standing 12 h the reaction mixture was filtered to yield 4-(2-hydroxyethylthio)-3,5-dimethylpyrazole (**8**) (2.5 g or 73%) of m.p. 162–163°. Recrystallization from isopropanol gave colorless prisms: m.p. 162–163°. N.m.r. (DMSO-d_6): 3.45 (2H, t, J = 7 Hz, CH_2O), 2.56 (2H, t, J = 7 Hz, CH_2S), 2.23 (6H, s, $2CH_3$); i.r. (KBr): 1565, 1040 cm^{-1}; u.v.: λ_{max} (MeOH) 235 nm (1520).

Anal. Calcd. for $C_7H_{12}N_2OS$: C, 48.80; H, 7.02; N, 16.26. Found: C, 48.64; H, 7.16; N, 15.86.

*N-(5,6-Dihydro-2-methyl-1,4-oxathiin-3-ylcarbonyl)-N′-phenylurea (**13**)*

To a mixture of sodium hydride (7.2 g, 0.3 mol) and *N*-phenylurea (41 g, 0.3 mol) in dry benzene (270 ml) and dimethylformamide (30 ml), which had been warmed and stirred for 1.5 h, was added dropwise over 25 min a solution of 5,6-dihydro-2-methyl-1,4-oxathiin-3-carbonyl chloride (**14**) (1*b*) in benzene prepared from the corresponding acid (50 g, 0.33 mol) and thionyl chloride. The reaction mixture was then stirred and heated under reflux for 1 h and finally let stand at room temperature overnight. It was washed with 5% aqueous sodium hydroxide, dried over sodium sulfate, and the solvent removed. The residual oil solidified and the solid was recrystallized three times from ethanol (charcoal) to give white crystals (10.4 g or 12%) of m.p. 120–123°. N.m.r. ($CDCl_3$): 10.57 (1H, s, NH, D_2O exchangeable), 8.84 (1H, s, NH, D_2O exchangeable), 7.3 (5H, m, aromatic), 4.35 (2H, m, CH_2O), 2.86 (2H, m, CH_2S), 2.25 (3H, s, CH_3).

Anal. Calcd. for $C_{13}H_{14}N_2O_3S$: C, 56.09; H, 5.07; N, 10.06. Found: C, 56.27; H, 5.24; N, 9.81.

*5-(2-Hydroxyethylthio)-6-methyl-1-phenyluracil (**15**)*

*(a) From Ethyl 5,6-Dihydro-2-methyl-1,4-oxathiin-3-carboxylate (**16**) and N-Phenylurea*

To a mixture of sodium hydride (8.4 g, 0.35 mol), *N*-phenylurea (40 g, 0.29 mol), and dry toluene (300 ml), which had been allowed to stand for 1 h, was added ethyl 5,6-dihydro-2-methyl-1,4-oxathiin-3-carboxylate (49.8 g, 0.27 mol) (1*b*). The mixture was heated under reflux. In about 45 min the solids dissolved almost completely and then precipitation began. The reaction mixture was stirred and heated under reflux for 2 h and subsequently let stand overnight; it was then treated with excess 5% aqueous sodium hydroxide and filtered. The aqueous phase was separated and acidified with concentrated hydrochloric acid. The precipitate was filtered, washed with water, dried, and washed with hot acetone and ethanol yielding a white solid (40.7 g or 55%) of m.p. 237–243°. Further purification by reprecipitation from aqueous sodium hydroxide followed by recrystallization from acetic acid yielded a product melting at 247.5–249°. N.m.r. (DMSO-d_6): 11.53 (1H, s, NH, D_2O exchangeable), 7.44 (5H, s, aromatic), 4.68 (1H, t, OH, D_2O exchangeable), 3.43 (2H, t, CH_2O), 2.73 (2H, t, CH_2S), 2.10 (3H, s, CH_3); i.r. (KBr): 3440, 1484, 1050, 760, 700 cm^{-1}.

Anal. Calcd. for $C_{13}H_{14}N_2O_3S$: C, 56.09; H, 5.07; N, 10.06. Found: C, 56.55; H, 5.27; N, 10.40.

*(b) From N-(5,6-Dihydro-2-methyl-1,4-oxathiin-3-ylcarbonyl)-N′-phenylurea (**13**)*

To a solution of *N*-(5,6-dihydro-2-methyl-1,4-oxathiin-3-ylcarbonyl)-*N′* phenylurea (**13**) (6.0 g, 0.022 mol) in dry toluene (40 ml) was added sodium hydride (0.6 g, 0.026 mol). The mixture was heated under reflux for 3 h, cooled to room temperature, and extracted with 5% aqueous sodium hydroxide (40 ml). The aqueous phase was separated after filtration and acidified with concentrated hydrochloric acid. The precipitate was collected, washed with water, and dried to yield a white solid (3.5 g or 57%) of m.p. 241–246°. The identity of this product with that obtained by method (*a*) was established by comparison of i.r. spectra and by m.m.p. determination.

5-(2-Hydroxyethylthio)-3,6-dimethyl-1-phenyluracil

5-(2-Hydroxyethylthio)-6-methyl-1-phenyluracil (**15**) was methylated in aqueous sodium hydroxide with dimethyl sulfate in the usual manner (11). The yield of the product after crystallization from toluene and from acetone – petroleum ether was 76%, m.p. 136–137.5°. N.m.r. ($CDCl_3$): 7.3 (5H, m, aromatic), 3.68 (3H, t, CH_2O + OH), 3.40 (3H, s, CH_3), 2.84 (2H, t, CH_2S), 2.28 (3H, s, CH_3).

Anal. Calcd. for $C_{14}H_{16}N_2O_3S$: C, 57.51; H, 5.51; N, 9.58. Found: C, 57.80; H, 5.76; N, 9.52.

5-(2-Chloroethylthio)-6-methyl-1-phenyluracil

To a stirred solution of 5-(2-hydroxyethylthio)-6-methyl-1-phenyluracil (**15**) (20 g, 0.068 mol) in chloroform (500 ml) was added over 40 min a solution of thionyl chloride (10 ml) in chloroform (50 ml). The reaction mixture was heated under reflux for 2 h, let stand overnight at room temperature, and filtered. The solvent and excess thionyl chloride were removed from the filtrate and the residue recrystallized from acetone and ethanol to yield a white solid (17.0 g or 84%) of m.p. 205–206.5°. N.m.r. (DMSO-d_6): 11.53 (1H, s, NH), 7.39 (5H, s, aromatic), 3.72 (2H, t, CH_2Cl) 2.99 (2H, t, CH_2S), 2.10 (3H, s, CH_3); i.r. (KBr): OH bands absent.

Anal. Calcd. for $C_{13}H_{13}ClN_2O_2S$: C, 52.60; H, 4.41; N, 9.44. Found: C, 52.99; H, 4.47; N, 9.03.

1-(5-Chloro-2-methylphenyl)-5-(2-hydroxyethylthio)-6-methyluracil

This was prepared from ethyl 5,6-dihydro-2-methyl-1,4-oxathiin-3-carboxylate (**16**) and *N*-(5-chloro-2-methylphenyl)urea as above. The product melted at 242–244° and the yield was 31%. N.m.r. (DMSO-d_6): 11.6 (1H, s, NH), 7.40 (3H, m, aromatic), 4.65 (1H, s, OH), 3.52 (3H, t, CH_2O), 2.77 (2H, t, CH_2S), 2.11, 2.07 (each 3H, s, CH_3).

Anal. Calcd. for $C_{14}H_{15}ClN_2O_3S$: C, 51.45; H, 4.62; N, 8.57. Found: C, 51.31; H, 4.58; N, 8.86.

*5,6-Dihydro-2-methyl-1,4-oxathiin-3-carboxylic Acid Hydrazide (**17**)*

A suspension of 5,6-dihydro-2-methyl-1,4-oxathiin-3-carboxylic acid (32 g, 0.2 mol) in thionyl chloride (20 ml, 0.28 mol) and benzene (200 ml) was heated at 70° until the solid dissolved. The reaction mixture was concentrated *in vacuo* to a syrup which was dissolved in chloroform (50 ml) and added dropwise to a stirred solution of hydrazine hydrate (85%, 100 ml) in chloroform (200 ml) cooled in an ice bath. After addition of the acid chloride was completed, the reaction mixture was kept at room temperature for 12 h before the chloroform layer was separated and extracted with cold 2.5 *N* hydrochloric acid (600 ml). The acidic aqueous extract was added to sodium bicarbonate (150 g) to give a weakly basic solution which was extracted with chloroform (2 × 200 ml). The chloroform extracts were combined and concentrated *in vacuo* to a syrup which was crystallized from ethanol to give the hydrazide (15.9 g or 46%) as colorless needles of m.p. 129.5–130.5°. N.m.r. (DMSO-d_6): 5.1 (3H, broad, NH), 4.2 (2H, m, CH_2O), 2.96 (2H, m, CH_2S), 1.97 (3H, s, CH_3); i.r. (KBr): 1650 cm^{-1} (CO).

Anal. Calcd. for $C_6H_{10}N_2O_2S$: C, 41.36; H, 5.79; N, 16.08. Found: C, 41.38; H, 5.80; N, 16.18.

*Rearrangement of 5,6-Dihydro-2-methyl-1,4-oxathiin-3-carboxylic Acid Hydrazide (**17**) to 4-(2-Hydroxyethylthio)-3-methyl-2-pyrazolin-5-one (**18**)*

A solution of 5,6-dihydro-2-methyl-1,4-oxathiin-3-carboxylic acid hydrazide (3.48 g, 0.02 mol) in *n*-butanol (20 ml) was heated under reflux for 24 h. The crystals, which formed on cooling, were filtered and washed with isopropanol to yield 4-(2-hydroxyethylthio)-3-methyl-2-pyrazolin-5-one (**18**) (2.85 g or 82%) of m.p. 187–189°. Recrystallization from ethanol gave colorless needles: m.p. 188–190°. N.m.r. (DMSO-d_6): 8.5 (3H, broad, NH + OH), 3.48 (2H, t, J = 7 Hz, CH_2O), 2.55 (2H, t, J = 7 Hz, CH_2S), 2.18 (3H, s, CH_3); i.r. (KBr): 2900–2600 cm^{-1} (zwitterion), 3420, 1030 cm^{-1} (primary OH); u.v.: λ_{max} (MeOH) 242 nm (2650).

Anal. Calcd. for $C_6H_{10}N_2O_2S$: C, 41.36; H, 5.79; N, 16.08. Found: C, 41.54; H, 5.84; N, 16.12.

*5,6-Dihydro-2-methyl-N-(2-pyridyl)-1,4-oxathiin-3-carboxamide (**20**) and 4H-3-(2-Hydroxyethylthio)-2-methylpyrido[1,2-a]pyrimidin-4-one (**21a**)*

A solution of 5,6-dihydro-2-methyl-1,4-oxathiin-3-carbonyl chloride (**14**) (1*b*) in benzene (prepared from the corresponding acid (16 g, 0.125 mol) in benzene (250 ml) and thionyl chloride (18 g, 0.152 mol)) was added dropwise over 2 h to a stirred mixture of 2-aminopyridine (9.4 g, 0.1 mol), triethylamine (10.2 g), and benzene (300 ml). The reaction mixture was kept at 4–5° during the addition and then left to stand at room temperature overnight. The precipitate (mainly $Et_3N.HCl$) was collected and washed thoroughly with hot benzene. The solvent was removed from the filtrate under reduced pressure and the residue placed in a funnel, pressed, and washed with a little cold acetonitrile. Two crystallizations from acetonitrile afforded compound **21***a* (12.2 g or 56%) of m.p. 109–111.5°. N.m.r. ($CDCl_3$): 8.93 (1H, d, aromatic), 7.95–7.00 (3H, complex, aromatic), 4.15 (1H, s, OH), 3.67 (2H, t, J = 6 Hz, CH_2O), 2.98 (2H, t, J = 6 Hz, CH_2S), 2.72 (3H, s, CH_3); i.r. (KBr): 3270, 1670, 1625 cm^{-1}; u.v.: λ_{max} (EtOH) 248 (11 500), 352 nm (14 300).

Anal. Calcd. for $C_{11}H_{12}N_2O_2S$: C, 55.93; H, 5.12; N, 11.86. Found: C, 55.98; H, 5.12; N, 11.80.

The hydrobromide of **21***a* was prepared by addition of 60% HBr to a solution of the base in acetone. Recrystallization from acetonitrile containing a little water gave crystals of m.p. 235–236° (dec.).

Anal. Calcd. for $C_{11}H_{13}BrN_2O_2S$: C, 41.65; H, 4.13; N, 8.83. Found: C, 41.39; H, 4.22; N, 8.87.

The combined acetonitrile washings and mother liquors from the purification of **21***a* were evaporated under reduced pressure and the residue dissolved in chloroform. The chloroform solution was washed with aqueous sodium bicarbonate and warm water and then dried over sodium sulfate. A small amount of **21***a* (0.4 g, m.p. 110–112°) was obtained from the aqueous washings. The solid material isolated from the chloroform solution was recrystallized from 95% ethanol to give the amide **20** (0.9 g or 4%) of m.p. 108.5–110°. N.m.r. ($CDCl_3$): 8.76 (1H, s, NH), 8.34–6.85 (4H, complex, aromatic), 4.36 (2H, m, CH_2O), 2.93 (2H, m, CH_2S), 2.25 (3H, s, CH_3); i.r. (KBr): 3160, 1670, 1655, 1600 cm^{-1}.

Anal. Calcd. for $C_{11}H_{12}N_2O_2S$: C, 55.93; H, 5.12; N, 11.86. Found: C, 55.73; H, 5.11; N, 11.93.

From the ethanolic mother liquors an additional amount of compound **21***a* was obtained (0.6 g, m.p. 109–111°).

*Stability of Compound **20** under the Reaction Conditions*

A solution of 0.83 g of the amide **20** in benzene (40 ml) containing triethylamine (0.5 g) was kept for 3 h at 5° and an additional 3 h at room temperature. The solvent and triethylamine were removed under reduced pressure. The residue, 0.80 g, melted at 106–109°; it was identified as **20** by i.r., n.m.r., and m.m.p.

Compounds ***24a***, ***24b***, ***25a***, ***25b***, and ***27***

The following procedure was used for the preparation of these compounds. To a stirred slurry or solution of the aminopyridine or 2-amino-4,6-dimethylpyrimidine (0.10 mol) in benzene (300 ml) containing triethylamine (10.2 g) was added dropwise over 1.5 h a solution of the acid chloride **14** (0.12 mol) in benzene (100 ml). The reaction mixture was kept at about 5° during the addition and then left to stand at room temperature overnight. The reaction mixture was filtered and the precipitate washed with benzene. The benzene was removed from the filtrate under reduced pressure and the residue purified by crystallization.

*4H-3-(2-Hydroxyethylthio-2,9-dimethylpyrido[1,2-a]-pyrimidin-4-one (**24a**)*

Yield: 10.2 g or 41%; m.p. 92–92.5° (Me_2CHOH); n.m.r. ($CDCl_3$): 8.88 (1H, d, aromatic), 7.80–6.95 (2H, complex, aromatic), 4.32 (1H, t, $J = 7$ Hz, OH), 3.88–3.45 (2H, m, CH_2O), 2.97 (2H, t, CH_2S), 2.74, 2.56 (each 3H, s, CH_3); i.r. (KBr): 3410, 1653, 1620 cm^{-1}.

Anal. Calcd. for $C_{12}H_{14}N_2O_2S$: C, 57.59; H, 5.64; N, 11.20. Found: C, 57.63; H, 5.83; N, 11.22.

The *O*-acetyl derivative of compound **24***a* was prepared by heating briefly on a steam bath a solution of **24***a* in pyridine with excess Ac_2O; m.p. 78.5–79° (petroleum ether).

Anal. Calcd. for $C_{14}H_{16}N_2O_3S$: C, 57.53; H, 5.52; N, 9.59. Found: C, 57.41; H, 5.52; N, 9.45.

*4H-3-(2-Hydroxyethylthio)-2,8-dimethylpyrido[1,2-a]-pyrimidin-4-one (**24b**)*

Yield: 12.2 g or 49%; m.p. 133–134° (benzene); n.m.r. ($CDCl_3$): 8.88 (1H, d, aromatic), 7.43–6.90 (2H, complex, aromatic), 4.05 (1H, s, OH), 3.65 (2H, t, CH_2O), 2.94 (2H, t, CH_2S), 2.72, 2.50 (each 3H, s, CH_3); i.r. (KBr): 3410, 1670, 1638 cm^{-1}.

Anal. Calcd. for $C_{12}H_{14}N_2O_2S$: C, 57.59; H, 5.64; N, 11.20. Found: C, 57.43; H, 5.77; N, 11.24.

The hydrobromide of **24***b* (prepared as that of **21***a*) was recrystallized from ethanol to give material of m.p. 222–223° (dec.).

Anal. Calcd. for $C_{12}H_{15}BrN_2O_2S$: C, 43.52; H, 4.56; N, 8.45. Found: C, 43.49; H, 4.69; N, 8.17.

The *O*-acetyl derivative of **24***b* (prepared as that of **24***a*) melts at 90–91° (petroleum ether – acetone).

Anal. Calcd. for $C_{14}H_{16}N_2O_3S$: C, 57.53, H, 5.52; N, 9.59. Found: C, 57.52; H, 5.46; N, 9.47.

*5,6-Dihydro-2-methyl-N-(6-methyl-2-pyridyl)-1,4-oxathiin-3-carboxamide (**25a**)*

Yield: 21.3 g or 85%; m.p. 87–89° (EtOH); n.m.r. ($CDCl_3$): 8.76 (1H, s, NH), 8.20–6.78 (3H, complex, aromatic), 4.36 (2H, m, CH_2O), 2.92 (2H, m, CH_2S), 2.43, 2.27 (each 3H, s, CH_3); i.r. (KBr): 3360, 1666 cm^{-1}.

Anal. Calcd. for $C_{12}H_{14}N_2O_2S$: C, 57.59; H, 5.64; N, 11.20. Found: C, 57.77; H, 5.78; N, 10.93.

The hydrobromide of **25***a* (prepared as that of **21***a*) was crystallized from acetone to give crystals of m.p. 178–179° (dec.).

Anal. Calcd. for $C_{12}H_{15}BrN_2O_2S$: C, 43.52; H, 4.56; N, 8.45. Found: C, 43.61; H, 4.59; N, 8.45.

*5,6-Dihydro-2-methyl-N-(4,6-dimethyl-2-pyridyl)-1,4-oxathiin-3-carboxamide (**25b**)*

Yield: 16.6 g or 63%; m.p. 128–129° (EtOH); n.m.r. ($CDCl_3$): 8.53 (1H, s, NH), 7.81 (1H, s, aromatic), 6.66 (1H, s, aromatic), 4.33 (2H, m, CH_2O), 2.91 (2H, m, CH_2S), 2.37, 2.29, 2.25 (each 3H, s, CH_3); i.r. (KBr): 3350, 1660 cm^{-1}.

Anal. Calcd. for $C_{13}H_{16}N_2O_2S$: C, 59.08; H, 6.10; N, 10.60. Found: C, 58.89; H, 6.23; N, 10.27.

The hydrobromide of **25***b* (prepared as that of **21***a*) melts at 170–170.5° (acetone).

Anal. Calcd. for $C_{13}H_{17}BrN_2O_2S$: C, 45.23; H, 4.96; N, 8.11. Found: C, 45.50; H, 4.92; N, 8.01.

*5,6-Dihydro-2-methyl-N-(4,6-dimethyl-2-pyrimidyl)-1,4-oxathiin-3-carboxamide (**27**)*

Yield: 8 g or 30%; m.p. 143–144° (acetone); n.m.r. ($CDCl_3$): 8.67 (1H, s, NH), 6.77 (1H, s, aromatic), 4.40 (2H, m, CH_2O), 2.98 (2H, m, CH_2S), 2.45 (6H, s, $2CH_3$), 2.29 (3H, s, CH_3); i.r. (KBr): 3220, 1680 cm^{-1}.

Anal. Calcd. for $C_{12}H_{15}N_3O_2S$: C, 54.33; H, 5.70; N, 15.84. Found: C, 54.69; H, 5.67; N, 15.63.

*4H-3-(2-Hydroxyethylthio)-2,7-dimethylpyrido[1,2-a]-pyrimidin-4-one (**24c**)*

To a stirred mixture of 2-amino-5-methylpyridine (10.8 g, 0.1 mol), triethylamine (10.5 g), and benzene (300 ml) was added dropwise over 2 h a solution of the acid chloride **14** (0.125 mol) in benzene (100 ml.). The reaction mixture was kept at 3–7° during the addition and then left to stand at room temperature overnight. The cooled reaction mixture was filtered and the precipitate treated with cold water (100 ml). The insoluble material was collected and dried in an oven under reduced pressure. Crystallization from ethanol–water (10:1) afforded crystals (8.8 g or 35%) of m.p. 122–123°. The benzene filtrate yielded an additional amount of product (1.5 g, m.p. 118–121°). N.m.r. ($CDCl_3$): 8.82 (1H, s, aromatic), 7.80–7.30 (2H, complex, aromatic), 3.65 (2H, t, CH_2O), 2.96 (2H, t, CH_2S), 2.73, 2.45 (each 3H, s, CH_3); i.r. (KBr): 3395, 1653, 1625 cm^{-1}.

Anal. Calcd. for $C_{12}H_{14}N_2O_2S$: C, 57.59; H, 5.64; N, 11.20. Found: C, 57.90; H, 5.40; N, 11.22.

The hydrobromide of **24***c* (prepared as that of **21***a*) was recrystallized from ethanol to give material of m.p. 239° (dec.).

Anal. Calcd. for $C_{12}H_{15}BrN_2O_2S$: C, 43.52; H, 4.56; N, 8.45. Found: C, 43.55; H, 4.54; N, 8.46.

The *O*-acetyl derivative of compound **24***c* (prepared as that of **24***a*) melts at 119–120° (petroleum ether).

Anal. Calcd. for $C_{14}H_{16}N_2O_3S$: C, 57.53; H, 5.52; N, 9.59. Found: C, 57.60; H, 5.61; N, 9.54.

*4H-3-(2-Hydroxyethylthio)-2-methylpyrimido[1,2-a]-pyrimidin-4-one (**26**)*

To a stirred mixture of 2-aminopyrimidine (9.5 g, 0.1 mol), triethylamine (10.2 g), and benzene (300 ml) was added dropwise over 1 h a solution of the acid chloride **14** (0.125 mol) in benzene (100 ml). The reaction mixture was kept at 3–5° during the first 2 h of the reaction and then left to stand at room temperature overnight. The precipitate was collected by filtration and washed with a little cold benzene. Then it was dissolved in water and the resulting solution basified with ammonia and extracted with chloroform. The extract was dried over sodium sulfate and the chloroform and triethylamine removed under reduced pressure. The crystalline residue (7.4 g) melted at 138–145°. Recrystallization from acetonitrile furnished crystals (5 g or 21%) of m.p. 150–152°. The

benzene filtrate and washings yielded an additional small amount of product (0.5 g, m.p. 147–150°). N.m.r. ($CDCl_3$): 9.37–8.99 (2H, complex, aromatic), 7.34–7.10 (1H, m, aromatic), 3.85–3.40 (3H, complex, CH_2O + OH); on addition of D_2O this absorption is replaced by a triplet, 2H, $J = 6$ Hz, CH_2O), 3.01 (2H, t, $J = 6$ Hz, CH_2S), 2.72 (3H, s, CH_3); i.r. (KBr): 3380, 1652, 1613 cm^{-1}.

Anal. Calcd. for $C_{10}H_{11}N_3O_2S$: C, 50.63; H, 4.67; N, 17.72. Found: C, 50.49; H, 4.63; N, 17.70.

The *O*-acetyl derivative of compound **26** (prepared as that of **24***a*) melts at 134–134.5° (petroleum ether – acetone).

Anal. Calcd. for $C_{12}H_{13}N_3O_3S$: C, 51.61; H, 4.69; N, 15.05. Found: C, 51.70; H, 4.72; N, 14.89.

Grateful acknowledgment is made to the National Research Council of Canada for financial assistance, to W. R. Boos, M. J. Ross, and W. P. Klimstra for providing the analyses and the n.m.r. and i.r. spectra, and to Dr. W. A. Harrison who carried out similar reactions with 2-aminothiazoles and participated in discussions.

1. (*a*) B. VON SCHMELING and M. KULKA. Science, **152**, 659 (1966). (*b*) B. VON SCHMELING, M. KULKA, D. S. THIARA, and W. A. HARRISON. U.S. patents 3,249,499 (1966), 3,393,202 (1968), 3,3o9,214 (1968), and 3,402,241 (1968); Can. patents 787,893 (1968), 791,151 (1968), 824,243 (1970), and 825,665 (1969).
2. G. E. WILSON. J. Am. Chem. Soc. **87**, 3785 (1965).
3. Z. YOSHIDA, H. OGOSHI, and T. TOKUMITSU. Tetrahedron, **26**, 2987 (1970).
4. A. J. HODGKINSON and B. STASKUN. J. Org. Chem. **34**, 1709 (1969).
5. J. M. STRALEY and A. C. ADAMS. Org. Synth. Coll. Vol. **4**, 415 (1963).
6. R. J. GROUT, B. M. HYNAM, and M. W. PARTRIDGE. J. Chem. Soc. C, 1590 (1969).
7. O. V. MATTSSON and B. E. BERTILSSON. German Offen. 2,133,450 (1972).
8. R. FUSCO. *In* The chemistry of heterocyclic compounds. Vol. 22. *Edited by* A. Weissberger. Interscience, New York and London. 1967. p. 54.
9. G. SCHRADER. U.S. patents 2,909,557 (1959) and 2,929,834 (1960).
10. J. F. WOLFE and G. B. TRIMITSIS. Can. J. Chem. **47**, 2097 (1969).
11. S. SENDA and A. SUZUI. Chem. and Pharm. Bull. (Tokyo), **6**, 476 (1958). Chem. Abstr. **53**, 10237*d* (1959).
12. G. DE STEVENS, A. HALAMANDARIS, P. WENK, and L. DORFMAN. J. Am. Chem. Soc. **81**, 6292 (1959).
13. H. ANTAKI and V. PETROW. J. Chem. Soc. 551 (1951).
14. R. ADAMS and I. J. PACHTER. J. Am. Chem. Soc. **74**, 4906 (1952).
15. R. ADAMS and I. J. PACHTER. J. Am. Chem. Soc. **74**, 5491 (1952).
16. I. J. PACHTER. J. Org. Chem. **26**, 4157 (1961).
17. G. R. LAPPIN. J. Org. Chem. **26**, 2350 (1961).
18. A. HALLEUX and H. G. VIEHE. J. Chem. Soc. C, 881 (1970).
19. C. F. H. ALLEN, H. R. BEILFUSS, D. M. BURNESS, G. A. REYNOLDS, J. F. TINKER, and J. A. VANALLAN. J. Org. Chem. **24**, 779 (1959).
20. A. MENDEL. J. Heterocycl. Chem. **9**, 935 (1972).
21. G. R. LAPPIN. J. Am. Chem. Soc. **70**, 3348 (1948).
22. G. R. LAPPIN, Q. R. PETERSEN, and C. E. WHEELER. J. Org. Chem. **15**, 377 (1950).
23. G. R. LAPPIN. J. Org. Chem. **23**, 1358 (1958).
24. J. J. D'AMICO. U.S. patent 2,704,791 (1955).
25. W. R. BOEHME. Org. Synth. Coll. Vol. **4**, 592 (1963).