[Chem. Pharm. Bull. 26(3) 722—735 (1978)]

UDC 547.869.2.04 : 542.943.6.04

Studies on Pyrimidine Derivatives and Their Related Compounds. XCI.[1] On the Oxidation Products of 2-Substituted-1,4-thiazin-3-one Derivatives

Akira Takamizawa, Hiroshi Harada, and Itsuo Makino

Shionogi Research Laboratory, Shionogi and Co., Ltd.[2]

(Received June 30, 1977)

On treatment of 2-*p*-chlorophenylthiazinothiamine (Ib) with hydrogen peroxide, 2-hydroxy-2-*p*-chlorophenylthiazinothiamine (IIb) was obtained. Similar reaction products of phenyl- and methylthiazinothiamine (Ia and Ie) were reinvestigated and found to be IIb analogues (IIa and IIe, respectively). Reactions of IIa, IIb or IIe with acetic anhydride afforded the corresponding N-(2-methyl-4-aminopyrimidin-5-yl)methyl -N-(2-acetylthio-4-amino-1-methyl-1-butenyl)aryl(or methyl)oxalamide (IIIa, IIIb or IIIe, respectively). Treatment of 2-*o*-tolylthiazinothiamine (Ic) with hydrogen peroxide gave N-[1-(2-oxido-1,2-oxathiolan-3-ylidene)ethyl]-N-[(2-methyl-4-aminopyrimidin-5-yl)methyl]-*o*-tolyloxalamide (VIIIc) as a major product and similar treatment of *o*-methoxyphenylthiazinothiamine (Id) with hydrogen peroxide gave 1-(2-methyl-4-aminopyrimidin-5-yl)methyl-2-methyl-3-(2-hydroxyethyl)-4-hydroxy-4-(2-methoxyphenyl)-Δ^2-pyrrolin-5-one (XV). Oxidations of Ia, Ic and Id with *m*-chloroperbenzoic acid also gave VIIIc and the corresponding VIIIc analogues (VIIIa and VIIId, respectively). The mechanisms of these reactions are discussed as shown in Chart 2.

Keywords——oxidation; desulfurization; α-ketoamido; 2-oxido-1,2-oxathiolane; substituent effect

In previous papers,[3–5] it was reported that oxidation of 2-phenyl-3-oxo-4-benzyl-5-methyl-6-(2-benzoyloxyethyl)-2,3-dihydro-4H-1,4-thiazine and 2-phenyl- or 2-methyl-4-(2-methyl-4-aminopyrimidin-5-yl)methyl-5-methyl-6-(2-hydroxyethyl)-3-oxo-2,3-dihydro-4H-1,4-thiazine (Ia, phenylthiazinothiamine or Ie, methylthiazinothiamine) with hydrogen peroxide yielded 2-hydroxy-2-phenyl-3-oxo-4-benzyl-5-methyl-6-(2-benzoyloxyethyl)-2,3-dihydro-4H-1,4-thiazine and 2-benzoyl- or 2-acethyl-2-hydroxy-3-(2-methyl-4-aminopyrimidin-5-yl)methyl-4-methyl-5-(2-hydroxyethyl)thiazoline (II'a or II'e), respectively. The structure of II'a was based on the following experimental results. The diacetate which was produced by the usual reaction of IIa with acetic anhydride was easily hydrolyzed to the original IIa under basic conditions, therefore both IIa and the diacetate were considered to have the same ring structures. The proton signals of the phenyl group of the diacetate in its nuclear magnetic resonance (NMR) spectrum showed a typical pattern of the benzoyl system in contrast to those of Ia. The diacetate underwent reduction to yield O-acetate of Ia on treatment with either sodium borohydride or lithium aluminum hydride. On oxidation with permanganic acid in acetic acid, IIa gave thiaminethiazolone and benzoic acid. When an aqueous hydrochloric acid solution of IIa was allowed to stand at room temperature, thiamine hydrochloride and benzoic acid were obtained in good yields.

These experimental data prompted us to investigate the effect of substituents, in particular *o*-substituents on the phenyl ring, which were presumed to exert steric hindrance and behave differently in the oxidation reactions of 2-arylthiazinothiamine derivatives with

1) Part XC: A. Takamizawa, Y. Matsushita, and H. Harada, *Chem. Pharm. Bull.* (Tokyo), **25**, 991 (1977).
2) Location: *Fukushima-ku, Osaka, 553, Japan.*
3) A. Takamizawa, H. Sato, and Y. Sato, *Chem. Pharm. Bull.* (Tokyo), **20**, 892 (1972).
4) A. Takamizawa, Y. Sato, and S. Tanaka, *Chem. Pharm. Bull.* (Tokyo), **14**, 588 (1966).
5) A. Takamizawa, Y. Mori, H. Sato, and S. Tanaka, *Chem. Pharm. Bull.* (Tokyo), **16**, 1773 (1968).

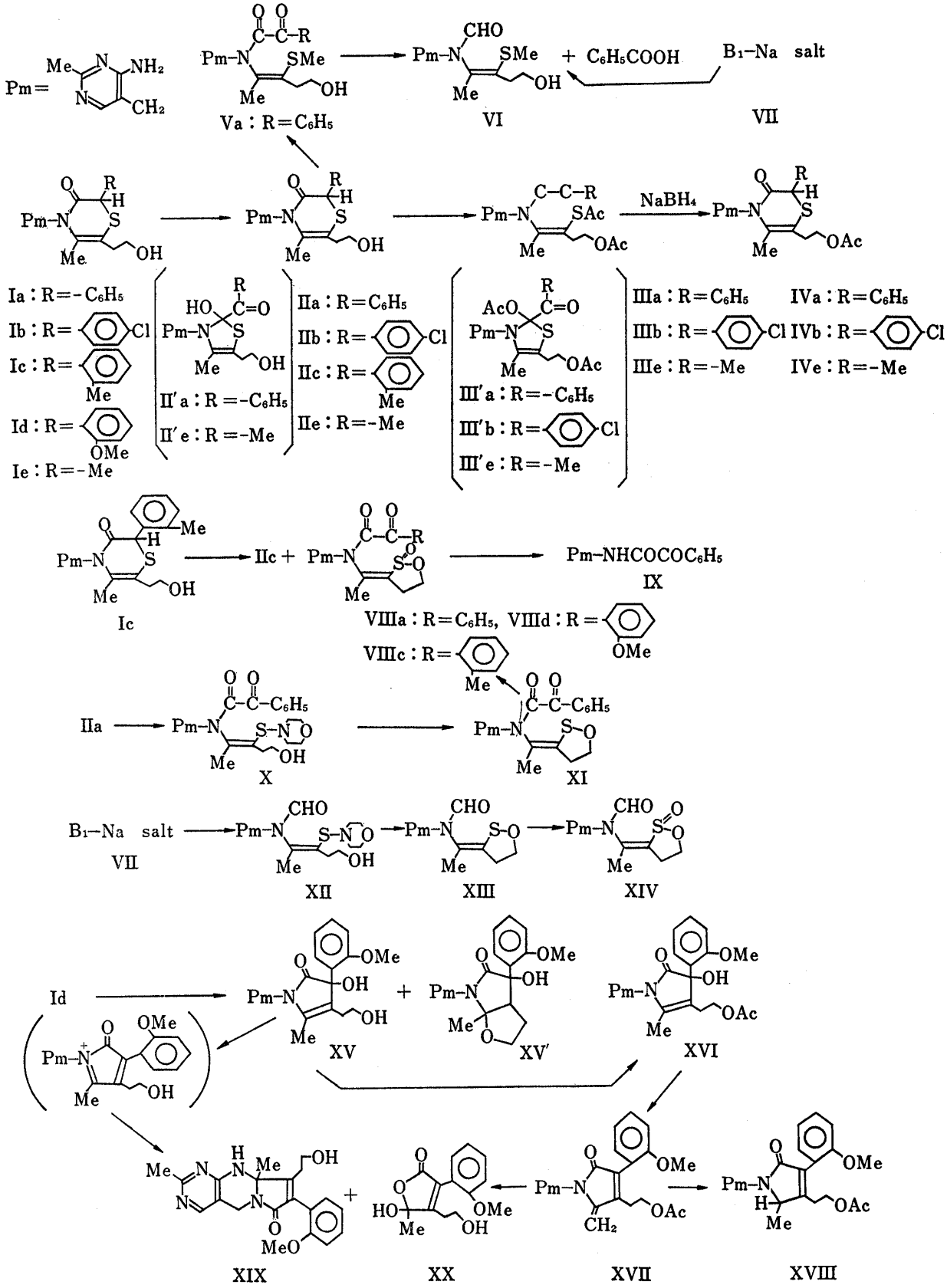


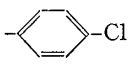
Chart 1

hydrogen paroxide. On the other hand, we[6] had synthesized a variety of corresponding 2-substituted thiazinothiamine analogues from the reactions of thiamine with several diethyl acylphosphonates.

At first, *p*-chlorophenyl-, *o*-tolyl- and *o*-methoxyphenylthiazinothiamine (Ib, c) were worked up for our serial studies. The oxidation of Ib with hydrogen peroxide gave a hydroxy compound with the expected yield, however the structure of this compound was not the expected pseudothiamine analogue but the 2-hydroxy-1,4-thiazine derivative (IIb) having the original six-membered ring system. Furthermore, the oxidation products (IIa, IIe) which had been obtained by the reaction of Ia and Ie with hydrogen peroxide and reported as pseudothiamine analogues (II'a, II'e) mentioned above, were also confirmed to be 2-hydroxy-1,4-thiazine analogues by reinvestigation. Also, the diacetates of IIa, IIb and IIe were thiol-type O,S-diacetates produced through ring cleavage of the 1,4-thiazine moiety under basic conditions and were not O,O'-diacetates of pseudothiamine analogues as we had reported in previous papers.[4,5] On the other hand, in similar reactions of Ic and Id with hydrogen peroxide, the hydroxylation at the C_2 position was markedly hindered and the sulfur atom was oxidized to give different compounds as major products. This paper deals with the above results in detail.

In the NMR spectrum (in $CDCl_3$) of the oxidation product (IIb) formed through similar reaction of Ib with hydrogen peroxide to that[4] of Ia, the aromatic proton signals of the *p*-chlorophenyl ring were observed at δ 7.44 as a singlet as shown in Table I, ruling out the benzoyl system. Thus the structure of IIb was not the expected pseudothiamine analogue

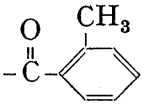
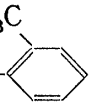
Table I. Physicochemical Data for Pm—N(C(=O)R)(C(OH))S—C(Me)=C(OH)

R	IR ν_{max}^{Nujol} cm^{-1}	UV λ_{max}^{EtOH} nm (log ε)	NMR δ (in d_6-DMSO)	MS *m/e*
	3390, 3320, 1660, 1640	231(4.17) 278(3.83)	1.92 (3H, s, >C=C(Me)–), 2.32 (3H, s, Pm–Me), 4.37—4.62 (1H, –CH(OH)–), 4.77 (2H, b, Pm–CH_2–), 6.68 (2H, b, –NH_2), 7.08 (1H, b, C_2–OH), 7.26—7.53 (5H, C_6H_5), 7.69 (1H, s, Pm–H)	105 ($\overset{+}{C}$OR)
	3280, 3120, 1670, 1640	226(4.39) 277(3.92)	1.94 (3H, s, >C=C(Me)–), 2.32 (3H, s, Pm–Me), 2.19—2.42 (2H, m, –CH_2–CH(O)–), 3.40 (2H, t, J=7 Hz, –CH(CH_2–O)–), 4.72 (2H, s, Pm–CH_2–), 6.67 (2H, b, –NH_2), 7.22 (1H, b, C_2–OH), 7.44 (4H, s, –C_6H_4–), 7.64 (1H, s, Pm–H)	139 ($\overset{+}{C}$OR)
	3420, 3320, 3160, 1640,	231(4.2) 277(4.03)	1.87 (3H, s, >C=C(Me)–), 2.30 (3H, s, C_6H_4–Me), 2.50 (3H, s, Pm–Me), 4.30—4.53 (1H, b, –CH(OH)–), 4.70—4.85 (2H, b, –CH_2–), 6.70 (2H, b, –NH_2), 6.98 (1H, s, C_2–OH), 7.13—7.43 (4H, –C_6H_4–), 7.72 (1H, s, Pm–H)	119 ($\overset{+}{C}$OR)
–CH_3	3360, 3100, 1660, 1655	223(4.14) 267(3.85)	1.60 (3H, s, –Me), 1.92 (3H, s, >C=C(Me)–), 2.28 (3H, s, Pm–Me), 4.23—4.45 (1H, b, –CH(OH)–), 4.55—4.70 (2H, Pm–CH_2–), 6.47 (1H, b, C_2–OH), 6.67 (2H, b, NH_2), 7.53 (1H, s, Pm–H)	43 ($\overset{+}{C}$OR)

6) A. Takamizawa, H. Sato, and I. Makino, *Vitamins* (Japan), **49**, 177 (1975).

but the 1,4-thiazine derivative having a hydroxyl group at the C_2 position. Thus, we reinvestigated the structure of IIa mentioned above. Its NMR spectrum (in DMSO-d_6) showed aromatic proton signals on the phenyl ring at δ 7.26—7.53 as a narrow band as shown in Table I, supporting the structure having a C–C_6H_5 system and no C–COC_6H_5 system. Treatment of IIa with sodium borohydride caused no reduction and IIa was recovered in a fairly good yield, ruling out the COC_6H_5 system. According to the above results, we concluded that the previous structure of a pseudothiamine analogue (II'a) was not correct and should be revised to 2-phenyl-2-hydroxythiazinothiamine. The NMR spectrum (in DMSO-d_6) of the diacetate which was formed by the reaction of IIb with acetic anhydride in pyridine showed aromatic proton signals on the *p*-chlorophenyl ring at δ 7.45, 7.72, 7.90 and 8.05 as an AB quartet complicated by second-order coupling, revealing that the benzoyl system was newly formed in this diacetate and that the structure of this compound might be the O,O'-diacetate of the pseudothiamine analogue (III'b) or the O,S-diacetate (IIIb) of the thiol-type compound which would be produced through ring cleavage of the 1,4-thiazine moiety of IIb by hydrolysis followed by the acetylation. The mass spectrum (MS) exhibited a fragmentation peak at *m/e* 429 due to $[M-SAc]^+$ suggesting that the structure was O,S-diacetate. Reduction of this compound with sodium borohydride afforded the O-acetate (IVa) of IIb, establishing the existence of the COC_6H_4Cl group in the diacetate as expected from the NMR spectrum. Treatment of this diacetate with 5% KOH solution readily reproduced IIb quantitatively at room temperature. On the other hand, the diacetate of IIa which had been synthesized by the reaction of IIa with acetic anhydride and had been reported as the O,O'-diacetate (III'a) of the pseudothiamine analogue mentioned above showed a mass ion peak at *m/e* 391 corresponding to $[M-SAc]^+$, suggesting that the structure might be the O,S-diacetate (IIIa) similar to that of IIb.

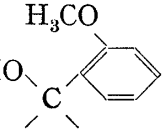
In order to prove the structure of these diacetates which were almost predictably S-substituted compounds from the experimental results, the reaction of IIa with dimethyl sulfate was carried out and a crystalline product (Va) was obtained. The product (Va) was supposed to be N-[(2-methyl-4-aminopyrimidin-5-yl)methyl]-N-(2-methylthio-4-hydroxy-1-methyl-1-butenyl)phenyloxalamide on the basis of its elemental analysis and NMR, infrared (IR), ultraviolet (UV) and mass spectral data (see Experimental). Treatment of Va with 5% KOH solution under mild conditions afforded S-methylthiamine (VI), which was identified with the authentic specimen prepared by the reaction of thiamine with dimethyl sulfate. Thus, it was ascertained that IIa gave S-substituted products by initiating ring fission of the 1,4-thiazine moiety followed by reaction of the newly formed thiol with electrophilic reagents. Accordingly, the diacetates of IIa and IIb obtained above could be O,S-diacetate derivatives (IIIa and b), respectively.

Similar oxidation of Ic with hydrogen peroxide gave two products; the structure of the minor product was confirmed to be 2-*o*-tolyl-2-hydroxythiazinothiamine (IIc) by elemental analysis and IR and NMR spectral data (see Experimental). Elemental analysis of the major product (VIIIc) gave the formula $C_{20}H_{24}N_4O_4S$, suggesting that increased oxidation of Ib would give VIIIc rather than IIc. The IR spectrum showed absorption bands of C=O groups at 1690 and 1660 cm^{-1} with the N–C=O system. The NMR spectrum (in $CDCl_3$) exhibited signals at 2.42 [3H, singlet, pyrimidine (Pm)–C_2–CH_3], 1.85 (3H, b, CH_3–C=C), 4.48—4.99 (4H, Pm–C_5–CH_2 and –CH_2–C=C–), 7.72 (2H, b, Pm–C_4–NH_2) and 7.93 (1H, s, Pm–C_6–H) and notable was the presence of aromatic proton signals on the phenyl ring at 7.20—7.88 as multiplet peaks, suggesting the  system. These data suggested a structure containing a N–COCO–  group and 1,2-oxathiolane-2-oxide moiety which would

be formed by cyclization derived from the dehydration between SH newly formed through ring fission of the thiazine moiety of IV and the thiazine–C_6–CH_2CH_2OH group.

Nakano *et al.*[7] have reported that treatment of S-morpholinothiamine with silicic acid afforded N-1-(1,2-oxathiolan-3-yliden)ethyl-N-(2-methyl-4-aminopyrimidin-5-yl)methylformamide (XIII) which was oxidized to give the corresponding S-oxide (XIV). Thus, we can predict that the corresponding S-morpholino derivative would be formed by a similar reaction of IIc with morpholine. The reaction of IIc with morpholine was carried out and the expected S-morpholino derivative (X) was obtained. The structure of X was confirmed on the basis of elemental analysis and IR and NMR spectra (see Experimental). Treatment of X with acetic acid afforded a crystalline product (mp 164—166°) whose structure was determined to be the corresponding 1,2-oxathiolane derivative (XI) by elemental analysis and IR and NMR spectra (see Experimental).

Oxidation of XI with *m*-chloroperbenzoic acid afforded the corresponding S-oxide which was identified with VIIIc mentioned above. Thus the structure of VIIIc was confirmed to be N-[1-(2-oxido-1,2-oxathiolan-3-ylidene)ethyl]-N-[(2-methyl-4-aminopyrimidin-5-yl)methyl]-*o*-tolyloxalamide. Compound VIIIc was also obtained by the oxidation of Ic with *m*-chloroperbenzoic acid in a lower yield. Similar oxidation of Ia and Id with *m*-chloroperbenzoic acid formed the corresponding VIIIc analogues (VIIIa and VIIId) in low yields, respectively.

Similar oxidation of *o*-methoxyphenylthiazinothiamine (Id) with hydrogen peroxide yielded two crystalline products; a major product (XV, mp 170—174°) from KOH extracts and a minor one (XV′, mp 212—214°) from $CHCl_3$ extracts. Elemental analysis of XV gave $C_{20}H_{24}N_4O_4$ without a sulfur atom, which was unexpected. The structure of XV was 1-(2-methyl-4-aminopyrimidin-5-yl)methyl-2-methyl-3-(2-hydroxyethyl)-4-hydroxy-4-(2-methoxyphenyl)-Δ^2-pyrrolin-5-one according to the following data. In the IR spectrum of XV, absorption due to the C=O group was observed at 1695 and 1960 cm^{-1}. The UV spectrum showed maxima at 223.5 nm (log ε 4.19) and 277 nm (log ε 3.99). The NMR spectrum (in DMSO-d_6, δ) showed peaks at 1.95 (3H, s, CH_3–C=C), 2.34 (3H, s, Pm–C_2–CH_3), 2.9—3.2 (2H, m, $C\underline{H}_2OH$), 3.52 (3H, s, OCH_3), 4.47 (2H, s, Pm–C_5–CH_2), 6.8 (2H, s, Pm–C_4–NH_2), 7.05—7.75 (4H, m, C_6H_4), 8.04 (1H, s, Pm–C_6–H) and 6.1 (1H, s, OH), the latter being shifted markedly to a lower field than those of IIa, IIb and IIc (7.08, 7.22 and 6.98, respectively, as shown in Table I) suggesting the existence of the  system on a different kind of ring system from the IIa analogue. The minor product XV′ was concluded to be an isomer of XV on the basis of elemental analysis (see Experimental) and the proton signal of 2-Me of XV′ in its NMR spectrum which appeared at δ 1.64 (3H, s). These data supported the structure of XV′ with a tetrahydrofuran ring system produced by cyclization of the hydroxyethyl group to the C_2–C_3 double bond. The acetylation of XV with acetic anhydride gave a sole monoacetate (XVI) which had an IR spectrum with an absorption band at 1735 cm^{-1} indicating a structure containing a O–$COCH_3$ group as expected.

Reaction of XVI with $POCl_3$ afforded a crystalline product (XVII, mp 191—193°) in fairly good yield. XVII was a dehydrate of XVI according to its elemental analysis with the molecular formula $C_{22}H_{24}N_4O_4$. The NMR spectrum (in DMSO-d_6, δ) showed peaks at 6.78 (2H, b, Pm–C_4–NH_2), 2.75 (2H, t, J=7 Hz, –$C\underline{H}_2$–CH_2–OAc) and 4.03 (2H, t, J=7 Hz, $CH_2C\underline{H}_2$–OAc). The NMR spectrum had proton signals due to C=CH_2 at 5.2 as a singlet and no proton signals corresponding to C=C–CH_3 and a tertiary OH group, showing that the dehydration reaction of XVI would occur between C=C–CH_3 and tertiary OH group to give an end methylene system in XVII. Compound XVII was catalytically reduced over 5%

7) J. Nakano and H. Nishimura, *Chem. Pharm. Bull.* (Tokyo), **19**, 705 (1971).

palladium-carbon to a crystalline product (XVIII, mp 141—143°), which according to elemental analysis corresponds to the formula $C_{22}H_{26}N_4O_4$, in 72% yield. In the NMR spectrum (in DMSO-d_6, δ) of XVIII, the proton signals of CH–C<u>H</u>$_3$ were observed at 1.33 as a typical doublet pattern (J=7 Hz) as expected. These findings confirmed the structures of XVI,

Table II. Physicochemical Data for Pm—N(Me)(=C(SCOMe)(CH$_2$OCOMe))—C(=O)—C(=O)—R

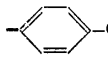
R	IR ν_{max}^{Nujol} cm^{-1}	UV λ_{max}^{EtOH} nm (log ε)	NMR δ (in d_6-DMSO)	MS *m/e*
	3390, 3300, 3120, 1740, 1700, 1660	243(4.22) 262(4.19)	1.92 (6H, s, COMe×2), 2.05 (3H, s, >C=C(Me)–), 2.32 (3H, s, Pm–Me), 4.63 (t, J=6 Hz, –CH$_2$–O), 4.37, 4.83 (2H, ABq, J=15 Hz, Pm–CH$_2$–), 6.77 (2H, b, –NH$_2$), 7.53—8.02 (5H, m, COC$_6$H$_5$)	395 [M–SAc]$^{+\cdot}$
	3480, 1740, 1710, 1685	237(sh)(4.17) 274(4.24)	1.95 (6H, s, COMe×2), 2.10 (3H, s, >C=C(Me)–), 2.33 (3H, s, Pm–Me), 4.67 (2H, t, J=6 Hz, –CH$_2$–O), 4.37, 4.70 (2H, ABq, J=15 Hz, Pm–CH$_2$–), 6.77 (2H, b, –NH$_2$), 7.45, 7.58, 7.72, 7.90, 8.05 (4H, m, –C$_6$H$_4$–)	429 [M–SAc]$^{+\cdot}$
–CH$_3$	3355, 3300, 3100, 1740, 1660, 1640	233(4.16) 278(3.89)	1.87 (3H, s, –COMe), 1.95, 1.97 (9H, s, COMe×2, >C=C(Me)–), 2.28 (3H, s, Pm–Me), 3.97—4.25 (2H, –CH$_2$–O), 4.58, 4.72 (2H, Pm–CH$_2$–), 6.65 (2H, b, –NH$_2$), 7.53 (1H, Pm–H)	

Table III. Physicochemical Data for Pm—N(Me)(=C(O–S(=O)–)—)—C(=O)—C(=O)—R

R	IR ν_{max}^{Nujol} cm^{-1}	UV λ_{max}^{EtOH} nm (log ε)	NMR δ (in d_6-DMSO)	MS *m/e*
	3300, 3080, 1690, 1675, 1665	238(4.16) 265(4.17)	2.03 (3H, b, >C=C(Me)–), 2.33 (3H, s, Pm–Me), 4.48, 4.95 (2H, ABq. J=16 Hz, Pm–CH$_2$–), 4.43—4.70 (2H, m, =C(S–O–CH$_2$)–), 6.75 (2H, b, –NH$_2$), 7.47—8.02 (5H, m, COC$_6$H$_5$)	336 [M–SO$_2$]$^{+\cdot}$ 267 [M–C(=O)–C(=O)–R]$^{+\cdot}$ 105 (COR)
	3340, 3300, 3120, 1690, 1660	236(4.14) 267(4.14)	1.85 (3H, b, >C=C(Me)–), 2.33 (3H, s, C$_6$H$_4$–Me), 2.42 (3H, s, Pm–Me), 4.48—4.98 (4H, Pm–CH$_2$, =C(S–O–CH$_2$)–), 6.72 (2H, b, –NH$_2$), 7.20—7.88 (4H, –COC$_6$H$_4$–), 7.93 (1H, s, Pm–H)	350 [M–SO$_2$]$^{+\cdot}$ 267 [M–C(=O)–C(=O)–R]$^{+\cdot}$ 119 (COR)
	3420, 3320, 3220, 1680(w), 1660	235(sh)(4.16) 268(4.11) 331(3.59)	1.77 (3H, b, >C=C(Me)–), 2.32 (3H, s, Pm–Me), 3.80 (3H, s, –OMe), 4.50—4.72 (4H, m, Pm–CH$_2$–, =C(S–O–CH$_2$)–), 6.73 (2H, b, –NH$_2$), 7.05—7.82 (4H, m, –C$_6$H$_4$–), 7.93 (1H, s, Pm–H)	366 [M–SO$_2$]$^{+\cdot}$ 267 [M–C(=O)–C(=O)–R]$^{+\cdot}$ 135 (COR)

XVII and XVIII as 1-(2-methyl-4-aminopyrimidin-5-yl)methyl-2-methyl-3-(2-acetoxyethyl)-4-hydroxy-4-(2-methoxyphenyl)-Δ^2-pyrrolin-5-one, 1-(2-methyl-4-aminopyrimidin-5-yl)methyl-2-methylene-3-(2-acetoxyethyl)-4-(2-methoxyphenyl)-Δ^3-pyrrolin-5-one, and 1-(2-methyl-4-aminopyrimidin-5-yl)methyl-2-methyl-3-(2-acetoxyethyl)-4-(2-methoxyphenyl)-Δ^3-pyrrolin-5-one, respectively.

Treatment of XV with 10% hydrochloric acid at 80° afforded a major product (XIX, mp 217—219°) and a minor one (XX, mp 124—126°). Elemental analysis of XIX gave the formula $C_{20}H_{22}N_4O_3$, indicative of the dehydrate of XV. The UV spectrum of XIX showed maxima at 234 and 288 nm, closely resembling that of thiamine free base[8] which showed maxima at 245 and 285 nm, suggesting that the pyrimidine nucleus of XIX might be part of the tricyclic system containing a tetrahydropyrimidopyrimidine moiety similar to that of thiamine free base. The IR spectrum of XIX showed an absorption band at 1700 cm^{-1} due to C=O group and the NMR spectrum (in $CDCl_3$, δ) showed peaks at 2.49 (3H, s, Pm–C_2–CH_3), 2.67 (2H, t, J=3 Hz, –C$\underline{H}_2$–CH_2–OH), 3.57 (3H, s, OCH_3), 3.87 (2H, m, $CH_2C\underline{H}_2OH$), 4.18, 5.22 (2H, ABq, J=17 Hz, Pm–C_5–CH_2), 6.85—7.43 (4H, m, C_6H_4) and 8.03 (1H, s, Pm–C_6–H). It can be generally recognized[9,10] that the proton signals of the C=C–CH_3 system of thiamine and related compounds are shifted to a lower field at δ value of about 1.85—2.2 as shown in Tables I, II, and III. In the case of XIX, however, the proton signals of the corresponding C–CH_3 group were shifted to a higher field (δ 1.68) as a singlet and that of Pm–C_4–NH was observed at 8.30 as a broad peak, strongly supporting the suggestion that in accordance with our earlier experiments,[8,11,12] the structure of XIX should contain a tricyclic ring moiety having a NH–$\overset{CH_3}{\overset{|}{C}}$–N system derived from intramolecular-cyclization between Pm–C_4–NH_2 and N–$\overset{CH_3}{\overset{|}{C}}$=C– group of pyrroline moiety followed by dehydration which occurred between C_3–OH and C_4–H on the pyrroline ring. The above data confirmed the structure of XIX to be 2,9a-dimethyl-8-(2-methoxyphenyl)-9-(2-hydroxyethyl)-5,7,9a,10-tetrahydropyrrolo[1′, 2′: 1,2]pyrimido[4,5-*d*]pyrimidin-7-one. Elemental analysis of the minor product (XX) gave the formula $C_{14}H_{16}OS$, suggesting that it lacks the pyrimidine moiety of XVI. The IR spectrum showed absorption bands at 3420 (OH), 3410 (OH) and 1730 cm^{-1} (C=O), the last band revealing that the S–C=O system should be ruled out. The mass spectrogram of XX exhibited a fragmentation peak at *m/e* 43 due to $^+COCH_3$, indicating that XX might be a structure having a –$COCH_3$ or HO–C–CH_3 group. The NMR spectrum (in $CDCl_3$, δ) exhibited signals at 1.77 (3H, s, C=C–CH_3), 2.50, 2.68 (2H, t of d, J=14 Hz, J=1 Hz, CH_2), 3.23 (1H, b, OH), 3.73, 3.75 (2H, m, CH_2), 3.77 (3H, s, OCH_3), 5.65 (1H, b, OH) and 6.92—7.53 (m, C_6H_4). These data strongly supported the suggestion that XX might be formed by cyclization through dehydration between the carboxylic acid and HO–C–CH_3 group which were derived from the successive hydrolysis of the $-N\begin{matrix}\diagup C-\\ \diagdown C-\end{matrix}$ system of XV. Accordingly, the structure of XX was established as 3-(2-methoxyphenyl)-4-(2-hydroxyethyl)-5-hydroxy-5-methyl-2,5-dihydrofuran-2-one.

Similar treatment of XVII with hydrochloric acid afforded XIX and XX in almost the same yields as those from XV, respectively. The structure of the reaction product (IIe),

8) A. Takamizawa, K. Hirai, T. Ishiba, and I. Makino, *Chem. Pharm. Bull.* (Tokyo), **19**, 759 (1971).
9) A. Takamizawa, S. Matsumoto, and S. Sakai, *Chem. Pharm. Bull.* (Tokyo), **17**, 128 (1969).
10) A. Takamizawa, S. Matsumoto, and S. Sakai, *Chem. Pharm. Bull.* (Tokyo), **17**, 343 (1969).
11) A. Takamizawa, K. Hirai, Y. Hamashima, Y. Matsumoto, and S. Tanaka, *Chem. Pharm. Bull.* (Tokyo), **16**, 1764 (1968).
12) A. Takamizawa and I. Makino, *Chem. Pharm. Bull.* (Tokyo), **22**, 1765 (1974).

which was formed by the reaction of methylthiazinothiamine (Ie) with hydrogen peroxide and reported to be 2-acetylpseudo-thiamine in our previous paper,[5] was revised to 2-methyl-2-hydroxy-4-(2-methyl-4-aminopyrimidin-5-yl)methyl-5-methyl-6-(2-hydroxyethyl)-3-oxo-2,3-dihydro-4H-1,4-thiazine on the basis of the following data. The NMR spectrum (in DMSO-d_6, δ) of IIe showed a signal at 1.6 as a singlet due to the thiazine-C_2–CH_3 which was too high for the CH_3CO system (δ 1.8—2.0), suggesting that the $-\overset{|}{\underset{|}{C}}-CH_3$ system in IIe was reasonable and the $CH_3CO-\overset{|}{\underset{|}{C}}-OH$ system should be ruled out. The structure of the diacetate (IIIe) obtained by the reaction of IIe with acetic anhydride in pyridine was also concluded to be N-[(2-methyl-4-aminopyrimidin-5-yl)methyl]-N-(2-acetoxythio-4-acetoxy-1-methyl-1-butenyl)-methyloxalamide on the basis of its physicochemical data shown in Table II.

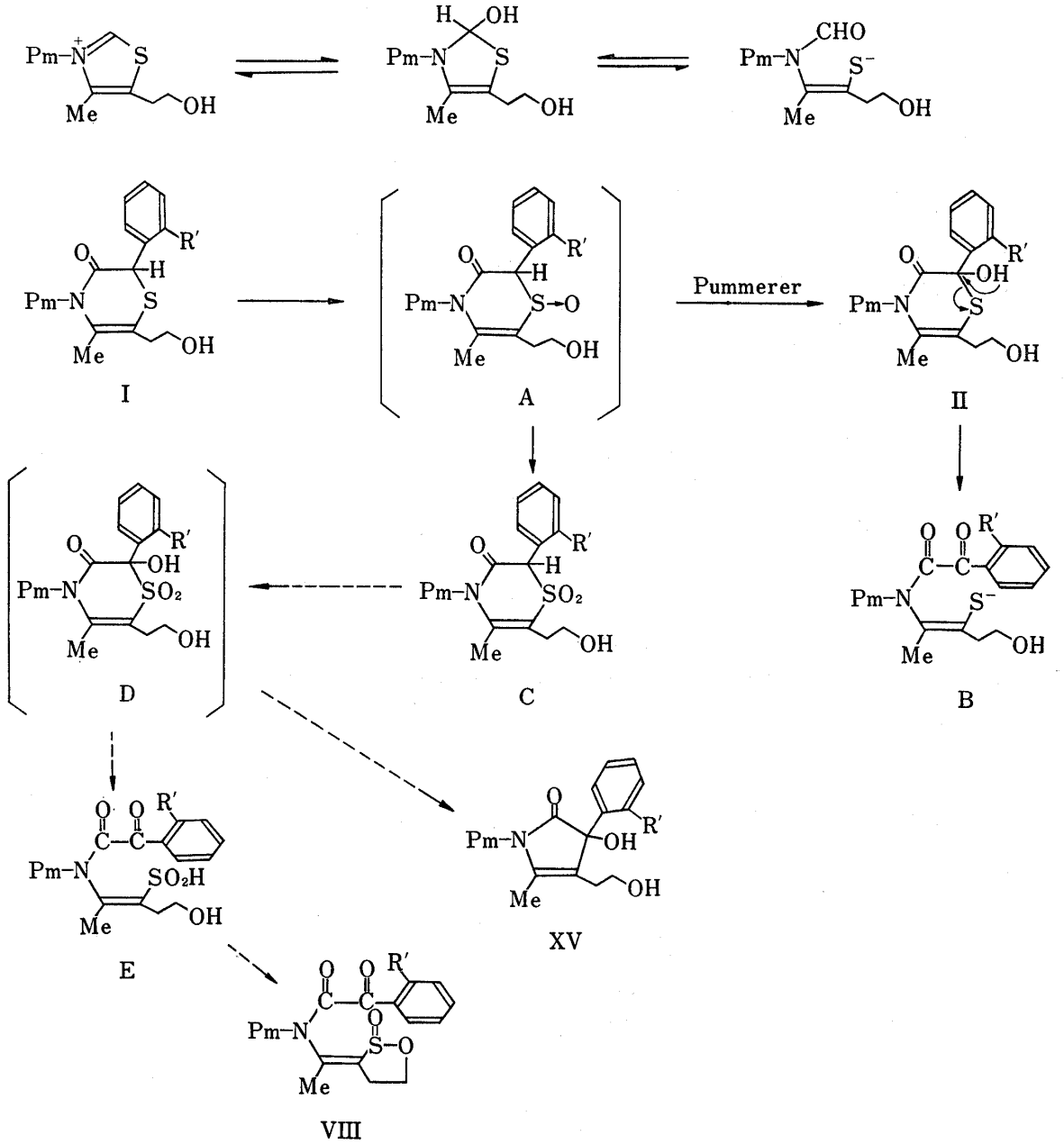


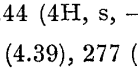
Chart 2

Although it is not possible to describe the reaction mechanisms of this series in detail, the approximate outline might be as shown in Chart 2. The Pummerer rearrangement of A to II is supported by the following experimental results. In the reactions of a couple of relatively simple 1,4-thiazine derivatives with hydrogen peroxide, we have isolated the corresponding sulfoxide compounds which rearranged into the corresponding 2-hydroxy-1,4-thiazine derivatives under mild conditions; details will be reported in later papers. On the formation of VIII, the *o*-substituent (R=CH_3, OCH_3) on the phenyl ring of A would hinder Pummerer rearrangement to the 2-hydroxy compound and successive oxidation of sulfoxide to form sulfone derivatives followed by hydroxylation at C_2-position to give D. Then the ring opening of D (R′=CH_3) would give the sulfinic acid compound (E) followed by dehydration to give VIII. On the other hand, VIII could not be obtained from II under a variety of oxidation conditions using H_2O_2 or *m*-chloroperbenzoic acid. Although it might be assumed to yield XV *via* D (R′=OCH_3), the mechanism of the formation of XV can not be explained reasonably. Further studies on the mechanism of this series are now in progress.

Experimental[13]

2-Aryl(or Alkyl)-2-hydroxy-4-[(2-methyl-4-aminopyrimidin-5-yl)methyl]-5-methyl-6-(2-hydroxyethyl)-3-oxo-2,3-dihydro-4H-1,4-thiazine (IIa—c, e)——General Procedure: A solution of 0.01 mol of Ia, b, c or e in a mixture of 15 g of AcOH and 0.011 mol of 30% H_2O_2 was stirred for 17 hr at room temperature. After evaporation of the solvent *in vacuo* at 30—35°, the residue was dissolved in $CHCl_3$ and the solution was extracted with 10% KOH under cooling. The KOH solution was washed with $CHCl_3$, and CO_2 was passed through it to saturation under ice cooling. The product that precipitated was recrystallized from EtOH.

2-Phenyl-2-hydroxy-4-[(2-methyl-4-aminopyrimidin-5-yl)-methyl]-5-methyl-6-(2-hydroxyethyl)-3-oxo-2,3-dihydro-4H-1,4-thiazine (IIa)——Yield 38.5%, colorless prisms, mp 197—198° (dec.). *Anal.* Calcd. for $C_{19}H_{22}N_4O_3S$ (386.469): C, 59.04; H, 5.74; N, 14.50; S, 8.30. Found: C, 59.06; H, 6.23; N, 14.46; S, 8.13. NMR (in d_6-DMSO, δ): 1.92 (3H, s, $\underline{Me}$>=<), 2.32 (3H, s, Pm–$\underline{Me}$), 4.37—4.62 (1H, ), 4.77 (2H, b, Pm–$C\underline{H}_2$–), 6.68 (2H, b, –$N\underline{H}_2$), 7.08 (1H, b, C_2–$O\underline{H}$), 7.26—7.53 (5H, $C_6\underline{H}_5$), 7.69 (1H, s, Pm–$\underline{H}$). IR ν_{max}^{Nujol} cm^{-1}: 3390, 3320, 1660, 1640. UV λ_{max}^{EtOH} nm (log ε): 231 (4.17), 278 (3.83). MS: *m/e* 105 ($\overset{+}{C}OC_6H_5$).

2-*p*-Chlorophenyl-2-hydroxy-4-[(2-methyl-4-aminopyrimidin-5-yl)methyl]-5-methyl-6-(2-hydroxyethyl)3-oxo-2,3-dihydro-4H-1,4-thiazine (IIb)——Yield 11.6%, colorless crystals, mp 169—170°. *Anal.* Calcd. for $C_{19}H_{21}ClN_4O_3$ (420.914): C, 54.22; H, 5.03; N, 13.31; O, 11.40; S, 7.62; Cl, 8.42. Found: C, 53.93; H, 5.01; N, 13.39; O, 11.69; S, 7.72; Cl, 8.22. NMR (in d_6-DMSO, δ): 1.94 (3H, s, $\underline{Me}$>=<), 2.32 (2H, s, Pm–$\underline{Me}$), 2.19—2.42 (2H, m, –$C\underline{H}_2$ ), 3.40 (2H, t, J=7 Hz, –$C\underline{H}_2$–O), 4.72 (2H, s, Pm–$C\underline{H}_2$), 6.67 (2H, b, –$N\underline{H}_2$), 7.22 (1H, b, C_2–$O\underline{H}$), 7.44 (4H, s, –$C_6\underline{H}_4$–), 7.64 (1H, s, Pm–$\underline{H}$). IR ν_{max}^{Nujol} cm^{-1}: 3280, 3120, 1670, 1640. UV λ_{max}^{EtOH} nm (log ε): 226 (4.39), 277 (3.92). MS *m/e*: 139 ().

2-*o*-Tolyl-2-hydroxy-4-[(2-methyl-4-aminopyrimidin-5-yl)methyl]-5-methyl-6-(2-hydroxyethyl)-3-oxo-2,3-dihydro-4H-1,4-thiazine (IIc)——Yield 1.2%, colorless crystals, mp 186—187° (dec.). *Anal.* Calcd. for $C_{20}H_{24}N_4O_3S\cdot 1/2EtOH$: C, 59.55; H, 6.43; N, 13.23; S, 7.57. Found: C, 59.37; H, 6.18; N, 13.12; S, 7.61. NMR (in d_6-DMSO, δ): 1.87 (3H, s, $\underline{Me}$>=<), 2.30 (3H, s, C_6H_4–$\underline{Me}$), 2.50 (3H, s, Pm–$\underline{Me}$), 4.30—4.53 (1H, b, ), 4.70—4.85 (2H, b, –$C\underline{H}_2$), 6.70 (2H, b, –$N\underline{H}_2$), 6.98 (1H, s, C_2–$O\underline{H}$), 7.13—7.43 (4H, –$C_6\underline{H}_4$–), 7.72 (1H, s, Pm–$\underline{H}$). IR ν_{max}^{Nujol} cm^{-1}: 3420, 3320, 3160, 1640, 1590. UV λ_{max}^{EtOH} nm (log ε): 231 (4.2), 277 (4.03). MS *m/e*: 119 ().

2-Methyl-2-hydroxy-4-[(2-methyl-4-aminopyrimidin-5-yl)methyl]-5-methyl-6-(2-hydroxyethyl)-3-oxo-2,3-dihydro-4H-1,4-thiazine (IIe)——Yield 34%, colorless prisms, mp 154—156°. *Anal.* Calcd. for $C_{14}H_{20}N_4O_3S\cdot H_2O$ (324.414): C, 49.10; H, 6.48; N, 16.36; O, 18.69; S, 9.37. Found: C, 49.34; H, 6.51; N, 16.19; O, 18.32; S, 9.52. NMR (in d_6-DMSO, δ): 1.60 (3H, s, C_2–$\underline{Me}$), 1.92 (3H, s, $\underline{Me}$>=<), 2.28 (3H, s, Pm–$\underline{Me}$), 4.23—4.45

13) NMR spectra were obtained with a Varian A-60 Spectrometer. The chemical shifts are reported in δ, using tetramethylsilane as reference. Multiplicities of signals are represented as s (singlet), d (doublet), t (triplet), q (quartet), b (broad) and m (multiplet). UV spectra were taken on a Hitachi EPS-3 spectrometer in 95% EtOH. IR spectra were taken on a Japan Spectroscopic Company IR-S spectrometer.

(1H, b, ⟋⟍⟋OH), 4.55—4.70 (2H, Pm–CH_2–), 6.47 (1H, b, C_2–OH), 6.67 (2H, b, –NH_2), 7.53 (1H, s, Pm–H). UV λ_{max}^{EtOH} nm (log ε): 223 (4.14), 267 (3.85). IR ν_{max}^{Nujol} cm^{-1}: 3360, 3100, 1660, 1655. MS *m/e*: 43 ($\overset{+}{C}OMe$).

N-[(2-Methyl-4-aminopyrimidin-5-yl)methyl]-N-(2-acetylthio-4-acetoxy-1-methyl-1-butenyl)aryl(or alkyl)oxalamide (IIIa, b, e)——General Procedure: To a solution of 1 mmol of IIa, b or e in 10 ml of dry pyridine, 5 mmol of Ac_2O was added. The solution was stirred for 4 hr at room temperature. After evaporation of the solvent *in vacuo*, the residue was treated with 1 N $NaHCO_3$ and the mixture was extracted with $CHCl_3$. The $CHCl_3$ solution was washed with H_2O, dried over Na_2SO_4 and evaporated. The residue was purified by SiO_2 column chromatography followed by recrystallization.

N-[(2-Methyl-4-aminopyrimidin-5-yl)methyl]-N-(2-acetylthio-4-acetoxy-1-methyl-1-butenyl)phenyloxalamide (IIIa)——Purified by SiO_2–AcOEt and recrystallized from AcOEt; yield 62%, colorless crystals, mp 160—162° (dec.). *Anal.* Calcd. for $C_{23}H_{26}N_4O_5S$ (470.544): C, 58.70; H, 5.57; N, 11.91; S, 6.81. Found: C, 58.67; H, 5.63; N, 11.69; S, 6.17. NMR (in d_6-DMSO, δ): 1.92 (6H, s, COMe×2), 2.05 (3H, s, >=⟍(Me)), 2.32 (3H, s, Pm–Me), 4.63 (t, J=6 Hz, ⟋⟍CH_2–O), 4.37, 4.83 (2H, ABq, J=15 Hz, Pm–CH_2–), 6.77 (2H, b, –NH_2), 7.53—8.03 (5H, m, COC_6H_5); (in $CDCl_3$, δ): 1.98 (6H, s, COMe×2), 2.08 (3H, s, >=⟍(Me)), 2.50 (3H, s, Pm–Me), 3.93 (2H, t, J=6 Hz, ⟋⟍CH_2–O), 4.38, 4.78 (2H, ABq, J=15 Hz, Pm–CH_2–), 6.15 (2H, b, –NH_2), 7.43—8.10 (5H, COC_6H_5). UV λ_{max}^{EtOH} nm (log ε): 243 (4.22), 262 (4.19). IR ν_{max}^{Nujol} cm^{-1}: 3390, 3300, 3120, 1740, 1700, 1660. MS *m/e*: 395 $[M-SAc]^+$, 105 $[COC_6H_5]^+$.

N-[(2-Methyl-4-aminopyrimidin-5-yl)methyl]-N-(2-acetylthio-4-acetoxy-1-methyl-1-butenyl)-*p*-chlorophenyloxalamide (IIIb)——Purified by SiO_2–AcOEt and recrystallized from AcOEt; yield 40%, colorless prisms, mp 172—174°. *Anal.* Calcd. for $C_{23}H_{25}ClN_4O_5S$ (504.989): C, 54.71; H, 4.99; N, 11.09; Cl, 7.02. Found: C, 54.74; H, 4.97; N, 10.96; Cl, 6.81. NMR (in d_6-DMSO, δ): 1.95 (6H, s, COMe×2), 2.10 (3H, s, >=⟍(Me)), 2.33 (3H, s, Pm–Me), 4.67 (2H, t, J=6 Hz, ⟋⟍CH_2–O), 4.37, 4.70 (2H, ABq, J=15 Hz, Pm–CH_2–), 6.77 (2H, b, –NH_2) 7.45, 7.58, 7.72, 7.90, 8.05 (4H, m, –C_6H_4–); (in $CDCl_3$, δ): 1.98 (3H, s, COMe), 2.02 (3H, s, COMe), 2.12 (3H, s, >=⟍(Me)), 3.93 (2H, t, J=6 Hz, ⟋⟍CH_2–O), 4.33, 4.80 (2H, ABq, J=15 Hz, Pm–CH_2–), 6.28 (2H, b, NH_2), 7.33, 7.37, 7.40, 7.87, 7.90, 7.93, 8.05 (5H, m, –C_6H_4, Pm–H). UV λ_{max}^{EtOH} nm (log ε): 237 (sh), (4.17), 274 (4.24). IR ν_{max}^{Nujol} cm^{-1}: 3480, 1740, 1710, 1685, 1630. MS *m/e*: 429 $[M-SAc]^+$.

N-[(2-Methyl-4-aminopyrimidin-5-yl)methyl]-N-(2-acetylthio-4-acetoxy-1-methyl-1-butenyl)methyloxalamide (IIIe)——Purified by SiO_2–$(CH_3)_2CO$: $CHCl_3$ (1: 1) and recrystallized from $(CH_3)_2CO$; yield 28%, colorless crystals, mp 143—145°. *Anal.* Calcd. for $C_{18}H_{24}N_4O_5S$: C, 52.93; H, 5.92; N, 13.72; O, 19.58; S, 7.85. Found: C, 53.23; H, 6.00; N, 13.57; O, 19.88; S, 8.03. NMR (in d_6-DMSO, δ): 1.87 (3H, s, COMe), 1.95, 1.97, 1.98 (9H, s×3, COMe×2, >=⟍(Me)), 2.28 (3H, s, Pm–Me), 3.97—4.25 (2H, ⟋⟍CH_2–O), 4.58, 4.72 (2H, Pm–CH_2–), 6.65 (2H, b, –NH_2), 7.53 (1H, Pm–H); (in $CDCl_3$, δ): 1.95 (3H, s, COMe), 1.98, 2.02 (3H×2, s, SCOMe, OCOMe), 2.10 (3H, s, >=⟍(Me)), 2.47 (3H, s, Pm–Me), 4.17 (2H, t, J=7 Hz, ⟋⟍CH_2–O), 4.37, 5.25 (2H, ABq, J=16 Hz, Pm–CH_2–), 5.92 (2H, b, –NH_2), 7.98 (1H, s, Pm–H). UV λ_{max}^{EtOH} nm (log ε): 233 (4.16), 278 (3.89). IR ν_{max}^{Nujol} cm^{-1}: 3355, 3300, 3100, 1740, 1660, 1640.

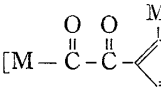
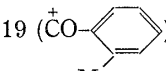
Reduction of IIIa, b, e with Sodium Borohydride——General Procedure: To a solution of 0.3 mmol of IIIa, b or e in 15 ml of abs. EtOH, 0.5 mmol of $NaBH_4$ was added. The solution was stirred for 3 hr, then allowed to stand overnight at room temperature. After evaporation of the solvent, the residue was dissolved in $CHCl_3$ and the solution was washed with H_2O, dried over Na_2SO_4 then evaporated. The residue was purified by chromatography and recrystallized. The crystals were identified by IR spectral comparison with an authentic sample. IVa: crystallized from $(C_2H_5)_2O$, yield 68%. IVb: purified by SiO_2–$(CH_3)_2CO$ column chromatography, yield 15.2%. IVe: purified by preparative thin-layer chromatography (PLC) [SiO_2–$CHCl_3$: $(CH_3)_2CO$ (3: 1)], yield 21.4%.

N-[(2-Methyl-4-aminopyrimidin-5-yl)methyl]-N-(2-methylthio-4-hydroxy-1-methyl-1-butenyl)phenyloxalamide (Va)——IIa (1.16 g, 3 mmol) in aqueous solution (20 ml) containing NaOH (429 mg, 12.3 mmol) was mixed with 776 mg (6.2 mmol) of Me_2SO_4 and the mixture was stirred for 3 hr at 10—15°. The aqueous layer was extracted with $CHCl_3$. The $CHCl_3$ layer was washed with H_2O, dried over anhyd. Na_2SO_4, then evaporated. The residual oil was crystallized from ether to yield 670 mg (53%) of Va. Recrystallization from acetone gave colorless prisms, mp 146—148°. *Anal.* Calcd. for $C_{20}H_{24}N_4O_3S$: C, 59.98; H, 6.04; N, 13.99; O, 11.99; S, 8.01. Found: C, 60.02; H, 6.31; N, 13.92; O, 11.94; S, 8.21. NMR (in d_6-DMSO, δ): 1.47 (3H, s, S–Me), 1.87 (3H, s, >=⟍(Me)), 2.32 (3H, s, Pm–Me), 2.13—2.38 (2H, –CH_2⟋⟍O), 3.02—3.38 (2H, ⟋⟍CH_2–O), 4.20, 4.72 (2H, ABq, J=15 Hz, Pm–CH_2–), 4.46—4.48 (1H, ⟋⟍⟋OH), 6.78 (2H, b, –NH_2), 7.37, 8.08 (5H, m, COC_6H_5), 7.92 (1H, s, Pm–H); (in $CDCl_3$, δ): 1.45 (3H, s, SMe), 2.02 (3H, s, >=⟍(Me)), 2.48 (3H, s, Pm–Me), 2.28—2.58 (2H, –CH_2⟋⟍), 3.57 (2H, t, J=7 Hz, ⟋⟍CH_2–O), 4.22, 4.95 (2H, ABq, J=15 Hz, Pm–CH_2–), 6.33 (3H, b, –NH_2), 7.28—7.63, 7.98—8.15 (5H, m, COC_6H_5), 7.83 (1H, s, Pm–H).

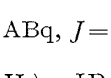
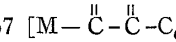
UV λ_{max}^{EtOH} nm (log ε): 249 (4.22), 256 (4.24). IR ν_{max}^{Nujol} cm^{-1}: 3420, 3320, 3200 (b), 1675, 1630, 1615. MS *m/e*: 353 $[M-SMe]^+$, 105 ($\overset{+}{C}OC_6H_5$).

S-Methylthiamine (VI)——Thiamine (VII) Na salt (3.04 g, 0.01 mol) in aqueous solution (30 ml) containing NaOH (0.4 g, 0.01 mol) was set aside at room temperature for 5 min. After addition of 2.56 g (0.02 mol) of Me_2SO_4 with stirring for 2 hr, MeOH was removed and the aqueous solution was extracted with $CHCl_3$. The $CHCl_3$ extract was washed with H_2O, dried over anhyd. Na_2SO_4, and evaporated. The residue was crystallized from ether to yield 700 mg (23.6%) of VI. Recrystallization from acetone gave colorless prisms, mp 192—194°. *Anal.* Calcd. for $C_{13}H_{20}N_4O_2S$: C, 52.68; H, 6.80; N, 18.90; O, 10.80; S, 10.82. Found: C, 52.62; H, 6.83; N, 18.83; O, 10.86; S, 10.97. NMR (in d_6-DMSO, δ): 1.90 (3H, s, S–Me), 1.93 (3H, s, ), 2.30 (3H, s, Pm–Me), 3.55 (2H, t, J=6 Hz, $-CH_2$〈O), 4.37 (2H, s, Pm–CH_2), 4.66 (1H, t, J=6 Hz, 〈OH), 6.65 (2H, b, $-NH_2$), 7.85 (1H, s, –N–CHO), 7.92 (1H, s, Pm–H); (in $CDCl_3$, δ): 1.90 (3H, s, S–Me), 2.0 (3H, s, ), 2.45 (3H, s, Pm–Me), 2.60 (2H, t, J=6 Hz, CH_2〈O), 3.77 (2H, t, J=6 Hz, 〈CH_2O), 4.47 (2H, b, Pm–CH_2–), 6.23 (2H, b, $-NH_2$), 7.83 (1H, s, N–CHO), 7.92 (1H, s, Pm–H). UV λ_{max}^{EtOH} nm (log ε): 238 (4.02), 273 (sh) (3.78). IR ν_{max}^{Nujol} cm^{-1}: 3320, 3220, 3120, 1670, 1650.

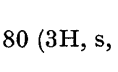
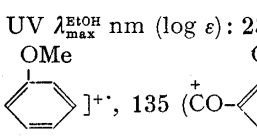
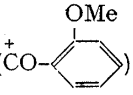
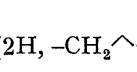
Treatment of Va with 5% KOH——A solution of 0.6 g (1.5 mmol) of Va in 20 ml of 5% KOH–EtOH was heated for 3.5 hr at 60°. The solution was concentrated and H_2O was added to the residue. The resulting solution was neutralized with 5% HCl–H_2O under ice cooling and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with H_2O, dried over Na_2SO_4, evaporated *in vacuo*, and the residue was purified by PLC. The purified oil was crystallized from ether. Recrystallization from acetone gave 102 mg (23%) of VI, which was identified by IR spectrum with the VI obtained above. The aqueous layer was acidified to pH 2 with 5% HCl–H_2O then extracted with ether. The ether extract was removed under reduced pressure. The crystalline residue was washed with ether to yield 57 mg (31%) of benzoic acid, which was identified with an authentic sample by IR spectra comparison.

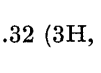
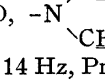
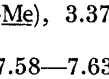
N-[1-(2-Oxido-1,2-oxathiolan-3-ylidene)ethyl]-N-[(2-methyl-4-aminopyrimidin-5-yl)methyl]-*o*-tolyloxalamide (VIIIc)——A solution of 5.7 g (15 mmol) of Ic in a mixture of 22 g of AcOH and 1.8 g of 30% H_2O_2 was stirred for 35 hr at room temperature. After evaporation of the solvent *in vacuo* at 30—35°, the residue was dissolved in $CHCl_3$ and extracted with 10% KOH under cooling. The $CHCl_3$ layer was washed with H_2O successively, dried over anhyd. Na_2SO_4, then evaporated. The residue was chromatographed on Al_2O_3 with ethyl acetate to give 0.874 g (14.6%) of VIIIc. Recrystallization from ethyl acetate gave colorless prisms, mp 179—182° (dec.). From the 10% KOH–H_2O layer, 0.076 g (1.2%) of IIc was obtained. *Anal.* Calcd. for $C_{20}H_{22}N_4O_4S$: C, 57.96; H, 5.35; N, 13.52; O, 15.44; S, 7.74. Found: C, 57.94; H, 5.48; N, 13.31; O, 15.91; S, 7.88. NMR (in d_6-DMSO, δ): 1.85 (3H, b, ), 2.33 (3H, s, C_6H_4–Me), 2.42 (3H, s, Pm–Me), 4.48—4.98 (4H, Pm–CH_2, ), 6.72 (2H, b, $-NH_2$), 7.2—7.88 (4H, $-COC_6H_4$–), 7.93 (1H, s, Pm–H). IR ν_{max}^{Nujol} cm^{-1}: 3340, 3300, 3120, 1690, 1660, 1640. UV λ_{max}^{EtOH} nm (log ε): 236 (4.14), 267 (4.14). MS *m/e*: 350 $[M-SO_2]^{+\cdot}$, 267 $[M-$  $]^{+\cdot}$, 119 ().

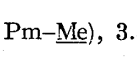
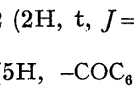
N-[1-(2-Oxido-1,2-oxathiolan-3-ylidene)ethyl]-N-[(2-methyl-4-aminopyrimidin-5-yl)methyl]aryloxalamide (VIII)——General Procedure: To a solution of 10 mmol of Ia, c or d in 150 ml of $CHCl_3$ was added 20 mmol of *m*-chloroperbenzoic acid in $CHCl_3$ under cooling. The solution was stirred at room temperature for 1 hr, then $CHCl_3$ was removed *in vacuo* at 30° and the residue was extracted with $CHCl_3$. The $CHCl_3$ extract was washed with 10% $NaHCO_3$ and H_2O, dried over anhyd. Na_2SO_4, and evaporated. The residue was purified by chromatography then recrystallized.

N-[1-(2-Oxido-1,2-oxathiolan-3-ylidene)ethyl]-N-[(2-methyl-4-aminopyrimidin-5-yl)methyl]phenyloxalamide (VIIIa)——Purified by Al_2O_3–AcOEt, recrystallization from AcOEt, yield 5.4%, colorless short needles, mp 156—158° (dec.). *Anal.* Calcd. for $C_{19}H_{20}N_4O_4S$: C, 56.99; H, 5.03; N, 13.99; S, 8.01. Found: C, 56.87; H, 4.92; N, 13.97; S, 8.29. NMR (in d_6-DMSO, δ): 2.03 (3H, b,), 2.33 (3H, s, Pm–Me), 4.48, 4.95 (2H, ABq, J=16 Hz, Pm–CH_2–), 4.43—4.70 (2H, m, ), 6.75 (2H, b, $-NH_2$), 7.47—8.02 (5H, m, COC_6H_5). IR ν_{max}^{Nujol} cm^{-1}: 3300, 3080, 1690, 1675, 1665, 1630. UV λ_{max}^{EtOH} nm (log ε): 238 (4.16), 265 (4.17). MS *m/e*: 336 $[M-SO_2]^+$, 267 $[M-$  $]^+$, 105 ($\overset{+}{C}OC_6H_5$).

N-[1-(2-Oxido-1,2-oxathiolan-3-ylidene)ethyl]-N-[(2-methyl-4-aminopyrimidin-5-yl)methyl]-*o*-tolyloxalamide (VIIIc)——Purified by Al_2O_3–AcOEt, recrystallization from AcOEt, yield 7.2%, colorless prisms, mp 179—182° (dec.), identified by IR spectrum with the VIIIc obtained above.

N-[1-(2-Oxido-1,2-oxathiolan-3-ylidene)ethyl]-N-[(2-methyl-4-aminopyrimidin-5-yl)methyl]-*o*-methoxyphenyloxalamide (VIIId)——Purified by SiO_2–$CHCl_3$: MeOH (5:1), recrystallization from $(CH_3)_2CO$, yield 3.3%, colorless prisms, mp 171—173° (dec.). *Anal.* Calcd. for $C_{20}H_{22}N_4O_5S$: C, 55.80; H, 5.15; N, 13.02; O, 18.58; S, 7.45. Found: C, 56.04; H, 5.32; N, 12.98; O, 18.82; S, 7.60. NMR (in d_6-DMSO, δ); 1.77 (3H, b, ), 2.32 (3H, s, Pm–Me), 3.80 (3H, s, –OMe), 4.5—4.72 (4H, m, Pm–CH_2, ), 6.73 (2H, b, –NH_2), 7.05—7.82 (4H, m, –C_6H_4–), 7.93 (1H, s, Pm–H). IR ν_{max}^{Nujol} cm^{-1}: 3420, 3320, 3220, 1680 (m), 1660. UV λ_{max}^{EtOH} nm (log ε): 235 (sh) (4.16), 268 (4.11), 331 (3.59). MS *m/e*: 430 (M^+), 366 [$M-SO_2$]$^+$, 267 []$^{+\cdot}$, 135 (), 122 (Pm–$\overset{+}{C}H_2$). NMR (in $CDCl_3$, δ); 1.83 (3H, triplet like broad, ), 2.50 (3H, s, Pm–Me), 2.57—3.05 (2H, –CH_2  O), 3.83 (3H, s, –OMe), 4.52—4.95 (2H, ), 4.40—5.22 (2H, ABq, J=15 Hz, Pm–CH_2–), 6.17 (2H, b, –NH_2), 6.88—7.93 (4H, m, COC_6H_4–), 7.98 (1H, Pm–H).

N-[(2-Methyl-4-aminopyrimidin-5-yl)methyl]-N-(2-morpholinothio-4-hydroxy-1-methyl-1-butenyl)phenyloxalamide (X)——IIa (1.29 g, 3.3 mmol) in aqueous MeOH (20 ml) containing NaOH (0.27 g, 6.75 mmol) was set aside at room temperature for 10 min. After morpholine (5.6 g, 64.3 mmol) had been added to the reaction mixture with stirring, an aqueous solution (10 ml) of I_2 (1.75 g, 6.9 mmol)–KI (1.83 g, 11 mmol) was added. Excess amine was removed and the aqueous solution was extracted with $CHCl_3$. The $CHCl_3$ extract was washed with a small amount of H_2O, dried over anhyd. Na_2SO_4, then evaporated. The residue was chromatographed on silica gel with acetone. The first eluate gave 0.98 g (62%) of X which was recrystallized from AcOEt, colorless prisms, mp 124—127° (dec.). *Anal.* Calcd. for $C_{23}H_{29}N_4O_4S$: C, 58.58; H, 6.20; N, 14.85; O, 13.57; S, 7.99. Found: C, 58.66; H, 6.02; N, 14.81; O, 13.87; S, 8.03. NMR (in d_6–DMSO, δ): 1.82 (3H, s, ), 2.32 (3H, s, Pm–Me), 3.20—3.47 (6H, CH_2  O, –N  O), 4.32, 4.68 (2H, ABq, J=14 Hz, Pm–CH_2–), 6.78 (2H, b, –NH_2), 7.53—8.07 (5H, COC_6H_5). (in $CDCl_3$, δ): 1.95 (3H, s, ), 2.33—2.67 (6H, CH_2  O, –N  O), 2.48 (3H, s, Pm–Me), 3.37—3.62 (6H, –CH_2O–, –N  O), 4.28, 4.70 (2H, ABq, J=14 Hz, Pm–CH_2), 6.37 (2H, b, –NH_2), 7.58—7.63, 7.97—8.13 (5H, COC_6H_5), 7.87 (1H, s, Pm–H). UV λ_{max}^{EtOH} nm (log ε): 239 (4.24), 252 (sh) (4.19). IR ν_{max}^{Nujol} cm^{-1}: 3390, 3310, 3200, 1675, 1645.

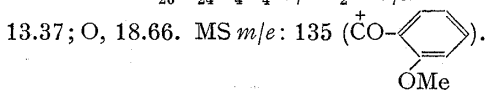
N-[1-(1,2-Oxathiolan-3-ylidene)ethyl]-N-(2-methyl-4-aminopyrimidin-5-yl)methyl Phenyloxalamide (XI)——A solution of X (0.8 g, 1.6 mmol) in $CHCl_3$ (25 ml) was treated with AcOH (3 ml) for 8 hr at room temperature. The $CHCl_3$ solution was washed with an $NaHCO_3$ and H_2O, dried over anhyd. Na_2SO_4 and evaporated. The residue was treated with ether to give 0.44 g (71%) of XI. Recrystallization from AcOEt gave colorless needles, mp 164—166° (dec.). *Anal.* Calcd. for $C_{19}H_{20}N_4O_3S$: C, 59.36; H, 5.24; N, 14.57; O, 12.48; S, 8.34. Found: C, 59.13; H, 5.13; N, 14.30; O, 12.19; S, 8.25. NMR (in d_6-DMSO, δ): 1.87 (3H, t, J=1 Hz, ), 2.35 (3H, s, Pm–Me), 3.87 (2H, t, J=6 Hz, ), 4.55 (2H, Pm–CH_2–), 6.73 (2H, b, NH_2), 7.53—7.95 (5H, m, COC_6H_5); (in $CDCl_3$ δ): 1.88 (3H, t, J=1 Hz, ), 2.50 (3H, s, Pm–Me), 2.42—2.72 (2H, ), 3.92 (2H, t, J=6 Hz, ), 4.47—4.65 (2H, Pm–CH_2–), 6.15 (2H, b, NH_2), 7.42—7.63, 7.87—8.02 (5H, –COC_6H_5), 7.90 (1H, s, Pm–H). IR ν_{max}^{Nujol} cm^{-1}: 3420, 3320, 3210, 1665. UV λ_{max}^{EtOH} nm (log ε); 251 (4.29). MS *m/e*: 384 (M^+), 105 ($\overset{+}{C}OC_6H_5$).

N-[1-(2-Oxido-1,2-oxathiolan-3-ylidene)ethyl]-N-[(2-methyl-4-aminopyrimidin-5-yl)methyl]phenyloxalamide (VIIIa)——A solution of XI (162 mg, 0.5 mmol) and *m*-chloroperbenzoic acid (87 mg, 0.5 mmol) in $CHCl_3$ (10 ml) was stirred for 15 min at room temperature. The $CHCl_3$ layer was washed with 10% $NaHCO_3$ and H_2O successively, dried over anhyd. Na_2SO_4, then evaporated. The residue was treated with AcOEt to give 57 mg (25%) of VIIIa, which was identified by IR spectra comparison with the VIIIa obtained above.

Treatment of VIIIa with 1 N KOH——A solution of 40 mg (0.1 mmol) of VIIIa in 3 ml of 1 N KOH in H_2O was stirred for 5 min at room temperature. The reaction mixture was extracted with $CHCl_3$. The $CHCl_3$ extract was washed with H_2O, dried over anhyd. Na_2SO_4, then evaporated. The residual crystals were washed with $(C_2H_5)_2O$ to give 15 mg (56%) of IX which was identified by IR spectra comparison with an authentic sample.

1-(2-Methyl-4-aminopyrimidin-5-yl)methyl-2-methyl-3-(2-hydroxyethyl)-4-hydroxy-4-(2-methoxyphenyl)-Δ^2-pyrrolin-5-one (XV) and 1-Methyl-2-(2-methyl-4-aminopyrimidin-5-yl)methyl-4-hydroxy-4-(2-methoxy-

phenyl)-2-aza-8-oxabicyclo[3,3,0]octan-3-one (XV′)——A solution of 2.02 g (5 mmol) of Id in a mixture of 7.5 g of AcOH and 1.2 g (10 mmol) of 30% H_2O_2 was stirred for 40 hr at room temperature, then AcOH was removed *in vacuo* at 30—35°. The oily residue was dissolved in 10% KOH, CO_2 was bubbled into the solution to adjust it to pH 8.6, then extraction was done with $CHCl_3$. The crystals separated from the aqueous layer were collected to give 0.503 g (22%) of XV. Recrystallization from EtOH gave crystals of mp 170—174° (dec.). NMR (d_6-DMSO, δ): 1.95 (3H, s, Me), 2.34 (3H, s, Pm–Me), 2.9—3.2 (2H, m, ⟋⟍CH_2–O), 3.52 (3H, s, OMe), 4.47 (2H, s, Pm–CH_2–), 6.10 (1H, s, C_4–OH), 6.80 (2H, s, NH_2), 7.07—7.75 (4H, m, –C_6H_4–), 8.04 (1H, s, Pm–H). IR ν_{max}^{Nujol} cm^{-1}: 1695, 1690, 1650. UV λ_{max}^{EtOH} nm (log ε): 223.5 (4.19), 277 (3.99). *Anal.* Calcd. for $C_{20}H_{24}N_4O_4 \cdot 1/5EtOH$: C, 62.20; H, 6.45; N, 14.23; S, 17.07. Found: C, 61.96; H, 6.45; N, 14.41; O, 17.57.

The $CHCl_3$ layer was washed with H_2O then dried over anhyd. Na_2SO_4. After removal of the solvent, the residual crystals were washed with H_2O to give 0.251 mg (11%) of XV′. Recrystallization from EtOH gave colorless prisms, mp 212—214° (dec.). NMR (in d_6-DMSO, δ): 1.64 (3H, s, C–Me), 2.32 (3H, s, Pm–Me), 3.57 (3H, s, O–Me), 3.43—3.70 (2H, m, ⟋⟍CH_2–O), 4.20, 4.30 (2H, Pm–CH_2–), 6.09 (1H, s, +OH), 6.82 (2H, NH_2), 6.88—7.77 (4H, m, –C_6H_4–), 8.02 (1H, s, Pm–H). IR ν_{max}^{Nujol} cm^{-1}: 3520, 3260, 3120, 1680. UV λ_{max}^{EtOH} nm (log ε): 221 (sh, 4.04), 235 (sh, 3.88), 277 (3.81). *Anal.* Calcd. for $C_{20}H_{24}N_4O_4 \cdot 1/2H_2O \cdot 1/2EtOH$: C, 60.56; H, 6.78; N, 13.45; O, 19.21. Found: C, 60.54; H, 6.83; N, 13.37; O, 18.66. MS *m/e*: 135 ().

1-(2-Methyl-4-aminopyrimidin-5-yl)methyl-2-methyl-3-(2-acetoxyethyl)-4-hydroxy-4-(2-methoxyphenyl)-Δ^2-pyrrolin-5-one (XVI)——To a solution of 384 mg (1 mmol) of XV in 8 ml of dry pyridine, 1 g of Ac_2O was added. The solution was stirred for 4 hr at room temperature. After evaporation of the solvent *in vacuo*, the residue was treated with 1 N $NaHCO_3$ then extracted with $CHCl_3$. The $CHCl_3$ solution was washed with H_2O, dried over anhyd. Na_2SO_4 then evaporated. The resulting crystals were recrystallized from $(CH_3)_2CO$ to yield 240 mg (57%) of XVI, mp 112—113°. NMR (d_6–DMSO, δ): 1.87 (3H, s, COMe), 1.95 (3H, s, C–Me), 2.33 (3H, s, Pm–Me), 3.52 (3H, s, OMe), 4.47 (2H, Pm–CH_2–), 6.03 (1H, s, +OH), 6.78 (2H, b, NH_2), 6.95—7.26 (4H, m, –C_6H_4–), 8.03 (1H, s, Pm–H). NMR ($CDCl_3$, δ): 1.93 (3H, s, COMe), 2.07 (3H, s, Me), 2.50 (3H, s, Pm–Me), 3.35 (3H, s, –OMe), 3.73 (2H, t, J=7 Hz, ⟋⟍CH_2–O), 4.40, 4.67 (2H, ABq, J=16 Hz, Pm–CH_2–), 4.67—5.33 (1H, b, +OH), 6.45 (2H, b, –NH_2), 6.67—7.75 (4H, m, –C_6H_4–), 8.05 (1H, s, Pm–H). IR ν_{max}^{Nujol} cm^{-1}: 3320, 3070, 1735, 1710, 1690, 1600. UV λ_{max}^{EtOH} nm (log ε): 224 (4.18), 277 (3.96). *Anal.* Calcd. for $C_{22}H_{26}N_4O_5 \cdot 1/2H_2O$: C, 60.68; H, 6.25; N, 12.87. Found: C, 60.97; H, 6.17; N, 12.78.

1-(2-Methyl-4-aminopyrimidin-5-yl)methyl-2-methylene-3-(2-acetoxyethyl)-4-(2-methoxyphenyl)-Δ^3-pyrrolin-5-one (XVII)——A solution of 1.1 g (2.6 mmol) of XVI in 30 ml of $CHCl_3$ was mixed with 3.93 g (26 mmol) of $POCl_3$ in 30 ml of $CHCl_3$. The solution was refluxed for 5 hr, then concentrated *in vacuo* and the residue was treated with $(CH_3)_2CO$ to give 0.85 g (80%) of XVII. Recrystallization from $(CH_3)_2CO$ gave colorless needles, mp 191—193°. *Anal.* Calcd. for $C_{22}H_{24}N_4O_4$: C, 64.70; H, 5.92; N, 13.72; O, 15.66. Found: C, 64.84; H, 5.84; N, 13.61; O, 16.05. NMR ($CDCl_3$, δ): 1.90 (3H, s, COMe), 2.47 (3H, s, Pm–Me), 2.47 (3H, s, OMe), 2.78 (2H, t, J=7 Hz, –CH_2⟍O), 4.10 (t, J=7 Hz, ⟋⟍CH_2–O), 4.65 (2H, s, Pm–CH_2–), 5.12 (2H, s, >=CH_2), 6.20 (2H, b, NH_2), 6.88—7.52 (4H, m, –C_6H_4–), 8.15 (1H, s, Pm–H). NMR (in d_6- DMSO, δ): 1.83 (3H, s, COMe), 2.32 (3H, s, Pm–Me), 2.75 (2H, t, J=7 Hz, –CH_2⟍O), 3.75 (3H, s, –OMe), 4.03 (2H, t, J=7 Hz, ⟋⟍CH_2–O), 4.64 (2H, s, Pm–CH_2–), 5.20 (2H, s, >=CH_2), 6.78 (2H, b, –NH_2), 6.98—7.57 (4H, m, –C_6H_4–), 7.97 (1H, s, Pm–H). IR ν_{max}^{Nujol} cm^{-1}: 3350, 3310, 1735, 1690, 1630, 1600. UV λ_{max}^{EtOH} nm (log ε): 235 (4.23), 270 (4.21), 277 (4.22).

1-(2-Methyl-4-aminopyrimidin-5-yl)methyl-2-methyl-3-(2-acetoxyethyl)-4-(2-methoxyphenyl)-Δ^3-pyrrolin-5-one (XVIII)——XVII (204 mg, 0.5 mmol) was hydrogenated with 55 mg of 5% Pd-carbon in EtOH (20 ml) for 2 hr at room temperature (11.7 ml was absorbed). After filtration, the reaction mixture was concentrated under reduced pressure, leaving an oily residue which was extracted with $CHCl_3$. The $CHCl_3$ extract was washed, dried and concentrated. The residual oil was treated with ether to give 148 mg (72%) of XVIII. Recrystallization from ether–acetone gave colorless needles, mp 141—143°. *Anal.* Calcd. for $C_{22}H_{26}N_4O_4$: C, 64.38; H, 6.38; N, 13.65; O, 15.59. Found: C, 64.44; H, 6.46; N, 13.54; O, 15.76. NMR (in $CDCl_3$, δ): 1.43 (3H, d, J=7 Hz, ), 1.95 (3H, s, COMe), 2.48 (3H, s, Pm–Me), 3.78 (3H, s, –OMe), 4.08 (2H, t, J=7 Hz, ⟋⟍CH_2–O), 4.18, 4.78 (2H, ABq, J=15 Hz, Pm–CH_2–), 6.03 (2H, b, –NH_2), 6.83—7.40 (4H, m, –C_6H_4), 8.03 (1H, s, Pm–H). NMR (in d_6-DMSO, δ): 1.33 (3H, d, J=7 Hz, ), 1.88 (3H, s, COMe), 2.32 (3H, s, Pm–Me), 4.07 (3H, s, OMe), 4.02 (2H, t, J=7 Hz, ⟋⟍CH_2–O), 4.20, 4.63 (2H, ABq, J=16 Hz, Pm–CH_2–), 6.77 (2H, b, –NH_2), 6.93—7.53 (4H, m, –C_6H_4–), 8.02 (1H, s, Pm–H). IR ν_{max}^{Nujol} cm^{-1}: 3300, 3080, 1750, 1735, 1680, 1670, 1650. UV λ_{max}^{EtOH} nm (log ε); 218 (4.38), 281 (3.91).

2,9a-Dimethyl-8-(2-methoxyphenyl)-9-(2-hydroxyethyl)-5,7,9a,10-tetrahydropyrrolo[1′,2′: 1,2]pyrimido[4,5-*d*]pyrimidin-7-one (XIX) and 3-(2-Methoxyphenyl)-4-(2-hydroxyethyl-5-hydroxy-5-methyl-2,5-dihydrofuran-2-one (XX)——A solution of XV (1.5 g, 3.75 mmol) in 15 ml of 10% HCl–H_2O was stirred for 71 hr at 80°. After evaporation of H_2O *in vacuo*, the residue was extracted with ether. The ether extract was washed with H_2O, dried over anhyd. Na_2SO_4 and evaporated to give an oily residue which was treated with

ether to give 60 mg (6%) of XX. Recrystallization from ether gave colorless needles, mp 124—126°. The aqueous solution was neutralized with 10% $NaHCO_3$ under ice-cooling and the solution was extracted with $CHCl_3$. The $CHCl_3$ solution was washed with H_2O then dried over anhyd. Na_2SO_4. After removal of the solvent, the residue was chromatographed on the silica gel column. Elution with acetone afforded XIX (0.2 g, 14%). Recrystallization from acetone gave colorless prisms, mp 217—219°. XIX: NMR (in $CDCl_3$, δ): 1.68 (3H, s, Me), 2.49 (3H, s, Pm–Me), 2.67 (2H, diffused t, $J=3$ Hz, $-CH_2$⌒O), 3.57 (3H, s, OMe), 3.87 (2H, m, $-CH_2-O$), 4.18, 5.22 (2H, ABq, $J=17$ Hz, Pm–CH_2–), 6.85—7.43 (4H, m, $-C_6H_4-$), 8.03 (1H, s, Pm–H), 8.53 (1H, b, –NH). NMR (in d_6-DMSO, δ): 1.60 (3H, s, Me), 2.37 (3H, s, Pm–Me), 3.72 (3H, s, OMe), 3.52—3.70 (2H, $-CH_2-$), 4.22, 5.02 (2H, ABq, $J=17$ Hz, Pm–CH_2–), 4.58 (1H, t, $J=6$ Hz, ⌒OH), 6.93—7.52 (4H, m, $-C_6H_4-$), 8.08 (1H, s, Pm–H), 8.30 (1H, b, –NH). *Anal.* Calcd. for $C_{20}H_{22}N_4O_3$: C, 65.56; H, 6.05; N, 15.29; O, 13.10. Found: C, 65.31; H, 6.34; N, 15.14; O, 13.12. UV λ_{max}^{EtOH} nm (log ε): 234 (sh) (4.07), 288 (3.87). IR ν_{max}^{Nujol} cm^{-1}: 1700. XX: NMR (in $CDCl_3$, δ): 1.77 (3H, s, Me), 2.50, 2.68 (2H, t of d, $J=14$ Hz, 1 Hz, $-CH_2-O$), 3.23 (1H, b, –OH), 3.73, 3.75 (2H, m, $-CH_2-$), 3.77 (3H, s, OMe), 5.65 (1H, b, –OH), 6.92—7.53 (4H, m, $-C_6H_4-$). NMR (in d_6-DMSO, δ): 1.63 (3H, s, Me), 3.48 (2H diffused t, $J=7$ Hz, $-CH_2-$), 3.75 (3H, s, –OMe), 4.60 (1H, b, –OH), 6.83—7.52 (4H, m, $-C_6H_4-$). *Anal.* Calcd. for $C_{14}H_{16}O_5$: C, 63.62; H, 6.10; O, 30.27. Found: C, 63.63; H, 5.99; O, 29.82. IR ν_{max}^{Nujol} cm^{-1}: 3420, 3140, 1730. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3680, 3600, 1762. MS *m/e*: 43 ($\overset{+}{C}OMe$).

Treatment of XVII with 10% HCl-H_2O——A solution of XVII (0.102 g, 0.25 mmol) in 10 ml of 10% HCl–H_2O was stirred for 20 hr at 80°. After evaporation of H_2O *in vacuo*, the residue was extracted with $CHCl_3$. The $CHCl_3$ solution was washed with H_2O then dried over anhyd. Na_2SO_4. After removal of the solvent, the residue was chromatographed on silica gel with acetone to give 2 mg (3%) of XX from the first fraction. Identification was made by IR spectra comparison with the XX obtained above. The second fraction gave 14 mg (15.3%) of XIX, which was identified by IR spectra comparison with the XIX obtained above.