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Studies on Pyrimidine Derivatives and Their Related Compounds. LXXVIII.[1] Unusual Reactions of Thiamine Free Base with Some Electrophilic Reagents[2]

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Reaction of thiamine free base (I) with ethyl pyrocarbonate afforded the 1 : 1 adduct (VIII) which was hydrolyzed to IX *via* N–C bond cleavage of pyrimidopyrimidine nucleus of I. The reaction of I with ethyl chloroformate also afforded VIII, together with IX. On the other hand, the reaction of I with benzoyl chloride yielded dibenzoate (IV) as the major product and monobenzoate (V) as the minor product, these compound being analogues of IX. The mechanisms of these reactions are discussed as shown in Chart 2.

In our previous paper,[4] it was reported that thiamine free base (I) as a mixture of configurational isomers was prepared from thiamine sodium salt by reaction with carbon dioxide and that it underwent facile acetylation or phenylcarbamoylation to N-acetate (II) or N-phenylcarbamate (III) respectively.

This paper deals with the unusual reaction of I with some electrophiles such as benzoyl chloride, ethyl chlorocarbonate and ethyl pyrocarbonate. The reaction appeares to be a 1,2-addition of electrophiles to the C-S bond of the thiazolidine ring of the polycyclic heteroaromatic system the sulfur atom of which behaves as a nucleophile.

The dibenzoate (IV) as a major product and the monobenzoate (V) as a minor product were obtained from I by the reaction with benzoyl chloride under the usual reaction conditions. The ultraviolet (UV) spectrum of IV showed maxima at 240 (log ε 4.34) and 269 mμ (log ε 4.29) showing a marked hypsochromic shifts when compared with the spectrum of I which has maxima at 245 and 285 mμ. From this, it is evident that ring fission of the original pyrimidopyrimidine nucleus of I occurs on reaction with benzoyl chloride. The infrared (IR) spectrum showed an absorption band at 3179 cm^{-1} (NH), while absorption bands at 1690 (C=O) and 1670 (C–O) would suggest that a O–COC_6H_5 system, which is known to absorb in the 1700 cm^{-1} region, may be ruled out and that a structure containing N–COC_6H_5 or S–COC_6H_5 is reasonable. The nuclear magnetic resonance (NMR) spectrum of IV in deuterochloroform exhibited signals at τ 1.66 [s, 1H, pyrimidine (Pm)-C_6-H], 2.06—2.53 (m, 10H, $2\times C_6H_5$), 7.35 (s, 3H, Pm-C_2-CH_3) and 0.31 (b, 1H, NH), the latter being shifted to a markedly lower field providing a evidence for the existence of Pm-C_4-NH-COC_6H_5 system. Furthermore, the four protons of the thiazole (Th)-C_5-CH_2CH_2O system appeared as complicated patterns and the proton signals of Th-C_4-CH_3 were shifted to a higher field (τ 8.21), closely resembling those of I which appear at τ 8.45, while the corresponding signals for thiamine and its derivatives are at τ 7.5—7.8.[5,6] These data give strong support to the suggestion that the structure of IV should be N-(2-methyl-4-benzamidopyrimidin-5-yl)methyl-N-(2-methyl-3-benzoylthiotetrahydrofuran-2-yl)

1) Part LXXVII: A. Takamizawa and H. Harada, *Chem. Pharm. Bull.* (Tokyo), **21**, 770 (1973).
2) A part of this paper was presented at the 19th Annual Meeting of the Kinki Branch of the Pharmaceutical Society of Japan at Osaka, November 1969.
3) Location: *Fukushima-ku, Osaka, 553, Japan.*
4) A. Takamizawa, K. Hirai, T. Ishiba, and I. Makino, *Chem. Pharm. Bull.* (Tokyo), **19**, 759 (1971).
5) Takamizawa, S. Matsumoto, and S. Sakai, *Chem. Pharm. Bull.* (Tokyo), **17**, 128 (1969).
6) A. Takamizawa, S. Matsumoto, and S. Sakai, *Chem. Pharm. Bull.* (Tokyo), **17**, 343 (1969).

formamide, produced by the substitution of benzoyl chloride at amino and sulfhydryl groups generated by ring fission of the pyrimidopyrimidine and thiazole moieties of I respectively. Likewise, on the basis of IR, UV and NMR spectral data (see experimental) V was deduced to have the structure IV lacking the N-benzoyl group.

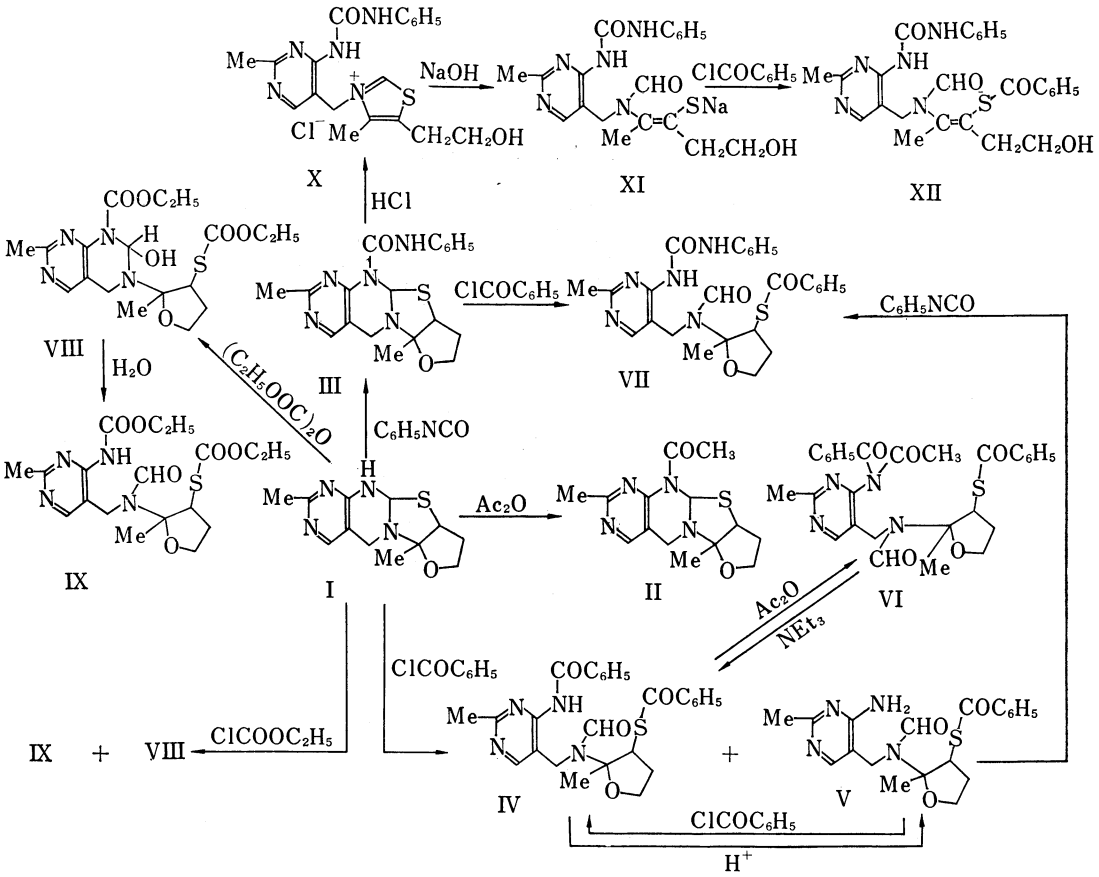
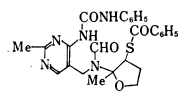
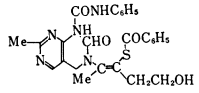


Chart 1

Reaction of V with benzoyl chloride under the usual conditions gave IV as expected; while treatment of IV with aqueous hydrochloric acid solution in ethanol afforded V. Therefore the structure of V could be established to be N-(2-methyl-4-aminopyrimidin-5-yl) methyl-N-(2-methyl-3-benzoylthiotetrahydrofuran-2-yl)formamide. Acetylation of IV with acetyl chloride gave the monoacetate of IV as an oily product (VI). The UV spectrum of VI showed maxima at 245 (log ε 4.37) and 260 mμ (log ε 4.32). Neither the IR nor the NMR spectra of VI showed absorption bands due to NH or NH_2 groups, and treatment of VI with triethylamine in ethanol readily regenerated IV. The structure of VI should therefore be N-[2-methyl-4-(N-benzoylacetamidopyrimidin-5-yl)methyl-N-(2-methyl-3-benzoylthiotetrahydrofuran-2-yl)formamide. Next reaction of III with benzoyl chloride was carried out under the same reaction conditions and monobenzoate (VII) was obtained. The UV spectrum of VII showed maxima at 248 (log ε 4.38) and 275 mμ (log ε 4.33) suggesting that the structure of VII is similar to that of IV, VII was therefore assumed to be the N-phenylcarbamoylamino analogue of IV. VII was also obtained from the reaction of V with phenylisocyanate, confirming the mutual relation of V and VII. It was of particular interest to compare the physico

chemical properties of VII with those of N-[2-methyl-4-(3-phenylureido)-pyrimidine-5-yl] methyl-N-(1-methyl-2-benzoylthio-4-hydroxy-1-butenyl)formamide (XII), which was synthesised by reaction of benzoyl chloride with the sodium salt (XI) of N-phenylcarbamoylthiamine prepared from N-phenylcarbamoylthiamine chloride hydrochloride (X) by treatment with aqueous sodium hydroxide. The physico chemical data for VII and XII are listed in Table I. It is notable that the data for VII are for the most part similar to those for XII, though in the NMR spectrum there are marked differences between the proton signals due to the Th-C_4-CH_3 and Th-C_5-CH_2CH_2-O groups. The proton signal of Th-C_4-CH_3 of VII was shifted to higher field than that of XII; and the proton signals of the Th-C_5-CH_2CH_2-O group of VII were observed at τ value 5.75, 5.81, 5.60 and 7.73 as complicated patterns while those of XII were shifted to 6.26 and 7.28 as typical triplet patterns. These data evidently support a structure of VII having a tetrahydrofuran ring system produced by cyclization of the Th-C_4-CH_2CH_2-OH group to the Th-C_4-C_5-double bond, and having an S-COC_6H_5 group. Accordingly the structures of IV, V, VI and VII were incontrovertibly confirmed. The 1: 1 adduct (VIII) of I and ethyl pyrocarbonate was obtained under similar conditions to those of the reaction of I and benzoyl chloride mentioned above. The UV spectrum of VIII showed a maximum at 298 mμ, a slight bathochromic shift compared with that of I, suggesting that the structure of VIII is similar to that of I and that a dihydropyrimidopyrimidine moiety is retained. The IR spectrum showed absorption bands at 3225 (NH or OH), 1720 (C=O) and 1635 cm^{-1} (C=O).

TABLE I. Physicochemical Data for VII and XII

Comp. No.	 VII	 XII
mp (°C)	162—163°	133—135° (decomp.)
UV spectrum λ_{max}^{EtOH} mμ (log ε)	248(4.381)	244(4.40)
	275(4.331)	278(4.27)
IR spectrum cm^{-1}	3200(NH), 1709(C=O)	3200(NH), 1713(C=O)
	1650(C=O)	—1653(C=O)
NMR spectrum in deuterochloroform. τ value	1.98(s,1H, Pm-C_6-H)	1.55(b, 1H, NH-C_6H_5)
	1.85(s, 1H, NCHO)	0.95(b, 1H, $NHCOC_6H_5$)
	0.57(b, H, $NHCOC_6H_5$)	1.85(s, 1H, NCHO)
	7.33(s, 3H, Pm-C_2-CH_3)	5.41(m, 2H, Pm-C_5-CH_2-N-)
	8.18(s, 3H, Th-CH_3)	6.26(t, 2H, J=6 cps, -$C\underline{H}_2$-$C\underline{H}_2$-OH)
	7.73(m, 2H, Th-C_5-$C\underline{H}_2$-CH_2-)	7.28(t, 2H, J=6 cps, -$\underline{H}C_2$-CH_2-OH)
		7.46(s, 3H, Pm-C_2-CH_3)
		7.73(s, 3H, Th-CH_3)

The NMR spectrum in deuterochloroform exhibited signals at τ values 1.25 (s, 1H, Pm-C_6-H), 7.5 (s, 3H, Pm-C_2-CH_3), 4.81, 6.58 (AB quartet, 2H, J=16 cps) and 8.53 (s, 3H, Th-C_4-CH_3), the latter being shifted to a higher field than that of VII which was shifted at τ value 8.15 as listed in Table I. It is notable that a coupled peak (d, 1H, J=1 cps) at τ value 3.65 was reduced to one-half its initial value and another coupled peak (d, 1H, J=1 cps) at 3.95 become a sharp pattern on treatment with D_2O, also notable that the NMR spectrum showed no proton signals of NH_2, NH or N–CHO. From these results, it is reasonable to assume that VIII has a CHOH system, dihydropyrimidine moiety, tetrahydrofuran nucleus, and N-$COOC_2H_5$ and S-$COOC_2H_5$ groups. On heating VIII in aqueous-alcohol at 60°, an isomer (IX) of VIII was obtained. The analysis of IX corresponded to that of VIII, $C_{18}H_{24}O_5N_4S$. Its UV spectrum exhibited maxima at 228 and 266 mμ showing a marked hypsochromic shift compared with the spectrum of VIII (298 mμ). On the basis of the above data, it is evident

that the ring fission of the dihydropyrimidopyrimidine neucleus of VIII occurred to give IX having a 4-aminopyrimidine system.

The IR spectrum of IX showed absorption bands at 1723 (C=O), 1702 (C=O) and 1647 cm^{-1} (C=O). The NMR spectrum of IX in deuterochloroform showed peaks at τ values 1.63 (s, 1H, Pm-C_6-H) and 7.33 (s, 3H, Pm-C_2-CH_3), a peak at 1.5 (s, 1H, NCHO) which was not observed with compound VIII, and a peak at 0.45 (s, 1H, NH) shifted to a much lower field and closely resembling that of IV mentioned above thereby supporting a structure of IX containing a Pm-C_4-NH-$COOC_2H_5$ system. On the other hand the proton signal of Th-CH_3 of IX found at τ value 8.26 support the existence of a tetrahydrofuran ring system in VIII.

Now it may be reasonably suggested that hydrolysis of the Pm-C_4-$\underset{\underset{H}{|}}{\overset{\overset{COOC_2H_5}{|}}{N}}$-C-OH system of VIII occurred to generate the Pm-C_4-$NHCOOC_2H_5$ and N-CHO system, thus, from the above experimental results the structures of VIII and IX are concluded to be 1-ethoxycarbonyl-2-hydroxy-3-(2-methyl-3-ethoxycarbonylthiotetrahydrofuran-2-yl)-7-methyl-1,2,3,4-tetrahydropyrimido[4.5-*d*]pyrimidine and N-(2-methyl-4-ethoxycarbonylaminopyrimidin-5-yl)methyl-N-(2-methyl-3-ethoxycarbonylthiotetrahydrofuran-2-yl)formamide respectively. VIII as a minor product and IX as a major product were also obtained from the reaction of I with ethyl chloroformate under the usual reaction conditions. The experimental information obtained in this work affords valuable elucidation of some mechanistic problems in our serial studies on the reactivity of thiamine free base.

Although it is not possible to describe the mechanisms of the reactions of this series in detail, they may be postulated as shown in Chart 2. Our interpretation is supported by the experimental result that compound VIII was obtained as an intermediate in the reaction of I with ethyl chloroformate to produce IX. As the polarization was further increased in a polar solvent such as DMF, the C-S bond fission of I should occur finally, the first step being the nucleophilic attack of sulfur anion at ethyl pyrocarbonate, followed by reaction of the O-$COOC_2H_5$ moiety with the carbocation adjacent to the sulfur atom of the thiazolidine ring to give a supposed compound XIV. Accordingly it might be concluded that a 1,2-addition reaction of I with ethyl pyrocarbonate proceeded, followed by rearrangement of the $COOC_2H_5$

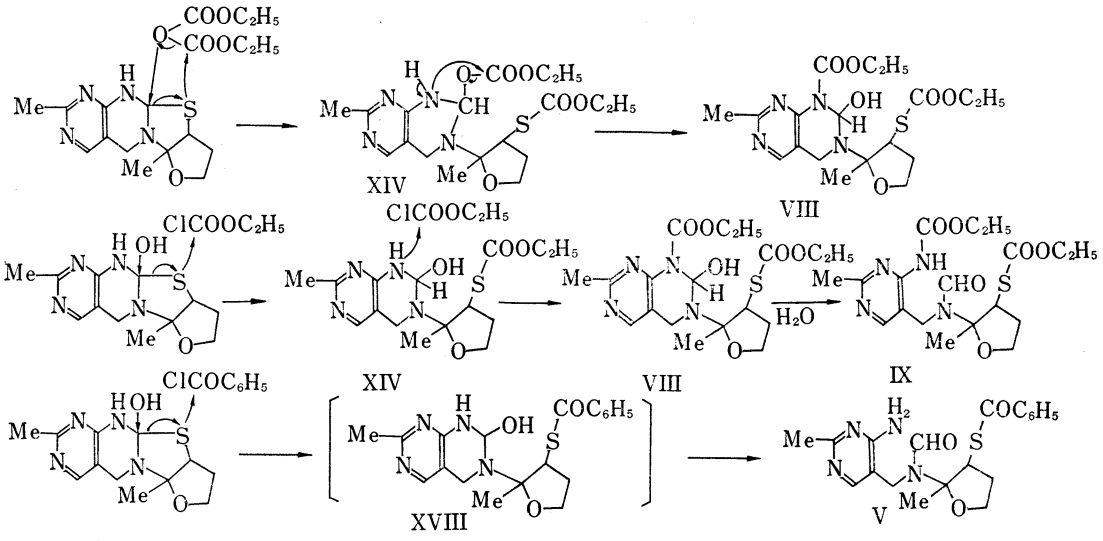


Chart 2

group bonding from oxygen to nitrogen to give VIII. In the reaction of I with ethyl chloroformate, nucleophilic attack of sulfur at the ethyl formate group might be followed by the combination of hydroxy anion with the carbocation adjacent to the sulfur of the thiazolidine moiety to give XIV; reaction of the NH group of XIV with another ethyl chloroformate might then occur to produce VIII, hydrolysed to give IX. The reaction of I with benzoyl chloride might be similar to that of I with ethyl chloroformate except that the supposed intermediate XVIII is too unstable to isolate and is hydrolyzed immediately to give IV. In this series we have obtained interesting results from the reaction of I with isocyanates and hope to report the work in detail in the following papers.

Experimental[7)]

Reaction of I with $ClCOC_6H_5$——To a suspension of 264 mg of I and 168 mg of $NaHCO_3$ in 20 ml of acetone 282 mg of $ClCOC_6H_5$ was added in ice-cooling. After stirring at room temperature for 12 hr, the reaction mixture was evaporated *in vacuo*, then the resulting residue was extracted with $CHCl_3$ and the extract was washed with H_2O, dried over anhyd. Na_2SO_4, and evaporated. Acetone was added to the oily residue to precipitate the starting materials as a colorless solid (42 mg), which was removed by filtration. The filtrate was subjected to column chromatography over silica gel and eluted with acetone. The first eluate gave 295 mg of N-(2-methyl-4-benzamidopyrimidine-5-yl)methyl-N-(2-methyl-3-benzoylthiotetrahydrofuran-2-yl)formamide (IV) which was recrystallized from acetone, mp 133—134°.

Anal. Calcd. for $C_{26}H_{26}O_4N_4S \cdot 1/2H_2O$: C, 62.50; H, 5.44; O, 14.41; N, 11.21; S, 6.41. Found: C, 62.35; H, 5.40; O, 14.25; N, 10.79; S, 6.39. UV λ_{max}^{EtOH} mμ (log ε): 240 (4.34), 269 (4.29). IR ν_{max}^{Nujol} cm^{-1}: 3179 (–NH), 3012 (–NH), 1690 (C=O), 1670 (C=O), 1650 (C=O). NMR (τ): 8.20 (s, 3H, Fu–C_2–CH_3), 7.33 (s, 3H, Pm–C_2–CH_3), 1.66 (s, 1H, Pm–C_6–H), 1.35 (s, 1H, N–CHO), −0.316 (b, H, NHCOC_6H_5).

From the second eluate was obtained of N-(2-methyl-4-aminopyrimidine-5-yl)methyl-N-(2-methyl-3-benzoylthiotetrahydrofuran-2-yl)formamide (V). Recrystallization from acetone gave prisms, mp 186—189°.

Anal. Calcd. for $C_{19}H_{22}O_3N_4S$: C, 59.06; H, 5.74; O, 12.42; N, 14.50; S, 8.28. Found: C, 58.94; H, 5.72; O, 12.73; N, 14.37; S, 7.76. UV λ_{max}^{EtOH} mμ (log ε): 239 (4.25), 271 (4.13). IR ν_{max}^{Nujol} cm^{-1}: 3307 (–NH), 3320 (–NH), 1668 (C=O). NMR (τ): 8.24 (s, 3H, Fu–C_2–CH_3), 7.58 (s, 3H, Pm–C_2–CH_3), 3.60 (b, 2H, Pm–C_4–NH_2), 1.83 (s, 1H, Pm–C_6–H), 1.65 (s, 1H, N–CHO).

N-[2-Methyl-4-(N-benzoylacetamidopyrimidin-5-yl)methyl]-N-(2-methyl-3-benzoylthiotetrahydrofuran-2-yl)formamide (VI)——To a solution of 985 mg of VI in 30 ml of pyridine, 176 mg of $ClCOCH_3$ was added under ice cooling. After stirring for 45 min under ice cooling the mixture was allowed to stand overnight at room temp., then stirred for 7 hr at 45°. The reaction mixture was evaporated *in vacuo*, the residue was extracted with $CHCl_3$, the $CHCl_3$ extract was washed with H_2O, dried over anhyd. Na_2SO_4, evaporated, and chromatographed on silica gel with acetone to give 141 mg of oily (VI) (13.2%).

Anal. Calcd. for $C_{28}H_{28}O_3N_4S$: C, 63.15; H, 5.30; O, 15.02; N, 10.52; S, 6.00. Found: C, 63.93; H, 5.37; O, 14.84; N, 10.36; S, 6.38. UV λ_{max}^{EtOH} mμ (log ε): 245 (4,37). 250 (4.36). IR ν_{max}^{Nujol} cm^{-1}: 1705 (C=O), 1664 (C=O). NMR (τ): 8.11 (s, 3H, Fu–C_2–CH_3), 7.53 (s, 3H, Pm–C_2–CH_3 or $COCH_3$), 7.50 (s, 9H, Pm–C_2–CH_3 or $COCH_3$), 1.43 (s, 1H, Pm–C_6–CH_3), 1.38 (s, 1H, NCHO).

N-(2-Methyl-4-aminopyrimidine-5-yl)methyl-N-(2-methyl-3-benzoylthiotetrahydrofuran-2-yl) formamide (V)——To a solution of 490 mg of IV in 30 mg of 99% EtOH, 5 mg of 5% HCl–EtOH was added to adjust the reaction mixture to pH 1 under ice cooling. After stirring for 7 hr the mixture was allowed to stand overnight at the room temperature. The reaction mixture was evaporated *in vacuo*, the residue was dissolved in water and extracted with benzene to remove impurities. The aqueous solution was adjusted to pH 7 with $NaHCO_3$ and then extracted with $CHCl_3$. The $CHCl_3$ extract was washed with H_2O, dried over anhyd. Na_2SO_4, evaporated *in vacuo*, and the residue was treated with acetone to give 41 mg (11%) of V. Recrystallization from acetone gave prisms, mp 186—189° (decomp.). Identified with V obtained above by IR spectra comparison.

N-(2-Methyl-4-benzamidopyrimidin-5-yl) methyl-N-(2-methyl-3-benzoylthiotetrahydrofuran-2-yl) formamido (IV)——(a) To a suspension of 150 mg of V and 65 mg of $NaHCO_3$ in 5 ml of pyridine, 109 mg of $ClCOC_6H_5$ was added with ice-cooling. After being stirred at 35—40° for 6 hr, the reaction mixture was evaporated *in vacuo* and the residue extracted with $CHCl_3$. The $CHCl_3$ extract was washed with H_2O, dried over anhyd. Na_2SO_4 and evaporated. The residue was treated with acetone to give 40 mg of IV (21%). Recrystallization from acetone gave prisms, mp 132—134°, identified with IV by IR spectra comparison.

(b) To a suspension of 533 mg of VI in 20 ml of 50% MeOH–H_2O, 101 mg of NEt_3 was added under ice cooling. After being stirred at room temperature for 4 hr, the reaction mixture was evaporated *in vacuo*

7) All melting points are uncorrected.

and the residue extracted with $CHCl_3$. The $CHCl_3$ extract was washed with H_2O, dried over anhyd. Na_2SO_4, evaporated, and chromatographed on silica gel with acetone to give 26 mg of IV (5.3%) mp 132—134° which was identified with IV by IR spectrum.

N-[2-Methyl-4-(3-phenylureido)pyrimidin-5-yl]methyl-N-(2-methyl-3-benzoylthiotetrahydrofuran-2-yl)-formamido (VII)——(a) To a suspension of 383 mg of III in 10 ml of pyridine 170 mg of $ClCOC_6H_5$ was added under ice cooling. After stirring at room temperature for 2 hr the reaction mixture was allowed to stand overnight. After evaporation of the reaction mixture *in vacuo*, the residue was extracted with $CHCl_3$ and the $CHCl_3$ extract was washed with H_2O, dried over anhyd. Na_2SO_4 and evaporated. Acetone was added to the resulting residue and insoluble material was removed to give 200 mg of recovered IIIa. The acetone solution was then concentrated and subject to column chromatography over silica gel, eluted with acetone to give 122 mg of VII (50.5%).

Anal. Calcd. for $C_{26}H_{27}O_4N_5S$: C, 61.77; H, 5.38; N, 13.86; O, 12.66; S, 6.33. Found: C, 61.61; H, 5.35; N, 13.80; O, 12.60; S, 6.48. UV λ_{max}^{EtOH} mμ (log ε): 248 (4.38), 275 (4.33). IR ν_{max}^{Nujol} cm^{-1}: 3200 (–NH), 1709 (C=O), 1675 (C=O). NMR (τ): 8.18 (s, 3H, Fu–C_2–CH_3), 7.33 (s, 3H, Pm–C_2–CH_3), 1.98 (s, 1H, Pm–C_6–H), 1.85 (s, 1H, NH–HO), 0.57 (b, 1H, NH).

(b) To a solution of 386 mg of V in 7 ml of DMF, 131 mg of $C_6H_5N{=}C{=}O$ was added. After stirring for 6.5 hr at room temperature the reaction mixture was allowed to stand overnight. The reaction mixture was evaporated *in vacuo*. The residue was extracted with $CHCl_3$ and the $CHCl_3$ extract was washed with H_2O, dried over anhyd. Na_2SO_4, evaporated, and chromatographed on silica gel with EtOAc to give 263 mg of recovered as the first fraction. From the second fraction was obtained 46 mg of VII (25%). Recrystallization from acetone gave prisms. mp 162—163° which was identified with VII by IR spectra comparison.

N-[2-Methyl-4-(3-phenylureido)pyrimidine-5-yl]methyl-N-(1-methyl-2-benzoylthio-4-hydroxy-1-butenyl)-formamide (XII)——To a suspension of 414 mg of the Na salt, prepared according to the general method from N-phenylcarbamoylthiamine chloridehydrochloride (XIV), in 10 ml of EtOH, 125 g of benzoyl chloride was added under ice cooling. After stirring for 2 hr the reaction mixture was evaporated *in vacuo*. The residue was extracted with $CHCl_3$. The $CHCl_3$ extract was washed with H_2O, dried over anhyd. Na_2SO_4, evaporated, and the oily residue was chromatographed on silica gel with acetone to give 88 mg of XVI (18.2%). Recrystallization from acetone–ether, mp 133—135° (decomp.).

Anal. Calcd. for $C_{26}H_{27}O_4N_5S$: C, 61.77; H, 5.38; N, 13.86; O, 12.66; S, 6.33. Found: C, 61.94; H, 5.18; N, 13.81; O, 12.93; S, 6.56.

1-Ethoxycarbonyl-2-hydroxy-3-(2-methyl-3-ethoxycarbonylthiotetrahydrofuran-2-yl)-7-methyl-1,2,3,4-tetrahydropyrimido[4,5-*d*]pyrimidine (VIII)——To a suspension of 3.96 g of I in 10 ml of dry pyridine, 9.72 g of $(COOC_2H_5)_2O$ was added at room temperature. After stirring for 1 hr, the reaction mixture was evaporated *in vacuo*. The residue was chromatographed on silica gel with acetone to give 1.08 g (26%) of VIII. Recrystallization from acetone gave prisms mp 160—163°.

Anal. Calcd. for $C_{18}H_{24}O_5N_4S{\cdot}H_2O$: C, 50.70; H, 6.15; N, 13.14; O, 22.50; S, 7.50. Found: C, 50.73; H, 6.08; N, 12.82; O, 22.18; S, 7.08. UV λ_{max}^{EtOH} mμ: 298. IR ν_{max}^{Nujol} cm^{-1}: 3225 (OH), 1723 (C=O), 1635 (C=O). NMR (τ): 8.53 (s, 3H, Fu–C_2–CH_3), 7.58 (s, 3H, Pm–C_2–CH_3), 3.65 (d, 1H, –CH–OH), 3.95 (d, 1H, CH–OH), 1.26 (s, 1H, Pm–C_6–H).

N-(2-Methyl-4-ethoxycarbonylaminopyridin-5-yl)methyl-N-(2-methyl-3-ethoxycarbonylthiotetrahydrofuran-2-yl)formamide (IX)——To a suspension of 213 mg of VIII in 10 ml of EtOH, 50.5 mg of NEt_3 was added, and the mixture was adjusted to pH 10. After stirring at 50° for 10 hr, the reaction mixture was evaporated *in vacuo*. The residue was extracted with $CHCl_3$ and the $CHCl_3$ extract was washed with H_2O, dried over anhyd. Na_2SO_4 and evaporated. The residue was chromatographed on silica gel with acetone to give 124 mg of IX (58%). Recrystallization from ether mp 114—115°.

Anal. Calcd. for $C_{18}H_{24}N_5O_5S{\cdot}H_2O$: C, 50.70; H, 6.12; N, 13.14; S, 7.50; O, 22.50. Found: C, 50.53; H, 6.09; N, 13.20; S, 7.63; O, 21.97. UV λ_{max}^{EtOH} mμ: 228, 266. IR ν_{max}^{Nujol} cm^{-1}: 1724 (C=O), 1702 (C=O), 1647 (C=O). NMR (τ): 8.26 (s, 3H, Fu–C_2–CH_3), 7.33 (s, 3H, Pm–C_2–CH_3), 1.63 (s, 1H, N–CHO), 1.50 (s, 1H, Pm–C_6H), 0.45 (b, 1H, NH).

Reaction of I with Ethyl Chlorocarbonate——To a suspension of 2.64 g of I and 840 mg of $NaHCO_3$ in 50 ml of acetone, 1.08 g of ClCOOEt was added under ice cooling. After stirring at room temperature for 12 hr, the reaction mixture was evaporated *in vacuo*. The resulting residue was extracted with $CHCl_3$ and the $CHCl_3$ extract was washed with water, dried over anhyd. Na_2SO_4 and evaporated. The oily residue was chromatographed over silica gel column with acetone to give crude VII from the first fraction, and recrystallization of the crude product from ether gave 73 mg of pure VIII, mp 150—153° (1.8%), which was identified with VIII obtained above by IR spectrum. From the second fraction was obtained 397 mg of IX. Recrystallization from ether gave prisms, mp 114—115°, identified with IX obtained above by IR spectrum.