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# Studies on Pyrimidine Derivatives and Their Related Compounds. LXXXVI.[1] Unusual Reactions of Thiamine Derivatives[2]

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Reaction of thiamine free base (I) with *p*-halobenzoyl chloride afforded diacylates (IIb,c) which were hydrolized to give mono-acylates (IIIb,c) under acidic conditions. On the other hand, the reaction of dibenzoate (IIa) and its *p*-haloanalogues (IIb,c) with triethylamine gave new compounds (IVa,b,c) which are the first examples of thiamine derivatives having a free SH group. The reaction of IVa,b,c with diazomethane afforded S-methyl derivatives (VIa,b,c). The mechanisms of these reactions are discussed as shown in Chart 2.

In a previous paper[4] we reported the unusual reaction of thiamine free base (I) with benzoyl chloride to give the dibenzoate (IIa) which was hydrolyzed under acidic conditions to the monobenzoate (IIIa) having the original ring system of IIa. This reaction behaviour prompted us to examine the reaction of I with *p*-chloro- and *p*-bromobenzoyl chloride, in which the relative electrophilicities are increased. The present paper gives experimental details of the formation of the *p*-chloro and *p*-bromo analogues (IIb, IIc) of IIa, which are also readily hydrolyzed to give the analogues (IIIb, IIIc) of IIIa under acidic conditions.

Furthermore this paper deals with the formation of a novel type of thiamine derivative containing a free SH group, produced by the reaction of IIa—c with triethylamine under usual conditions.

When I was allowed to react with *p*-chloro- or *p*-bromobenzoyl chloride, N-(2-methyl-4-*p*-chlorobenzamidopyrimidin-5-yl)methyl-N-(2-methyl-3-*p*-chlorobenzoylthiotetrahydrofuran-2-yl)formamide (IIb) or its *p*-bromoanalogue (IIc) was obtained respectively. IIb and IIc were concluded to be analogues of IIa on the basis of elemental analysis (see Experimental), ultraviolet (UV) spectrum, infrared (IR) spectrum, and nuclear magnetic resonance (NMR) spectrum as shown in Table I. Treatment of IIb or IIc with a solution of hydrogen chloride in aqueous ethanol gave IIIb or IIIc as colourless crystals. These were established to be N-(2-methyl-4-aminopyrimidin-5-yl)methyl-N-(2-methyl-3-*p*-chlorobenzoylthiotetrahydrofuran-2-yl)formamide or its *p*-bromo analogue, analogues of IIIa, by elemental analysis, UV, IR, and NMR data (Table I).

When IIa was treated with triethylamine in 50% aqueous ethanol solution at room temperature, colourless crystals (IVa, mp 193—195°) were isolated as the main product. The elemental analysis of IVa corresponds to a formula $C_{19}H_{22}O_3N_4S$, suggesting that it is a isomer of IIIa. The UV spectrum of IVa exhibits maxima at 232 (log $\varepsilon$ 4.26) and 283 nm (3.62) showing a marked bathochromic shift compared with the spectrum of IIIa which has maxima at 239 (4.25) and 271 nm (4.13), and showing similarity to that of I which has maxima at 245 (3.96) and 285 nm (3.84). From this, it is evident that IVa has a different ring system from IIIa, and a structure having a tetrahydropyrimidopyrimidine moiety might be expected. The IR spectrum shows absorption bands at 3280 (NH), 1650 (C=O) and 1730 $cm^{-1}$ (C=O), the

1) Part LXXXV: A Takamizawa and H. Sato, *Chem. Pharm. Bull.* (Tokyo), **22**, 1526 (1974).
2) A part of this paper was presented at the 90th Annual Meeting of the Pharmaceutical Society of Japan at Sapporo, July 1970.
3) Location: *Fukushima-ku, Osaka, 553, Japan.*
4) A. Takamizawa, I. Makino, and S. Yonezawa, *Chem. Pharm. Bull.* (Tokyo), **21**, 285 (1973).

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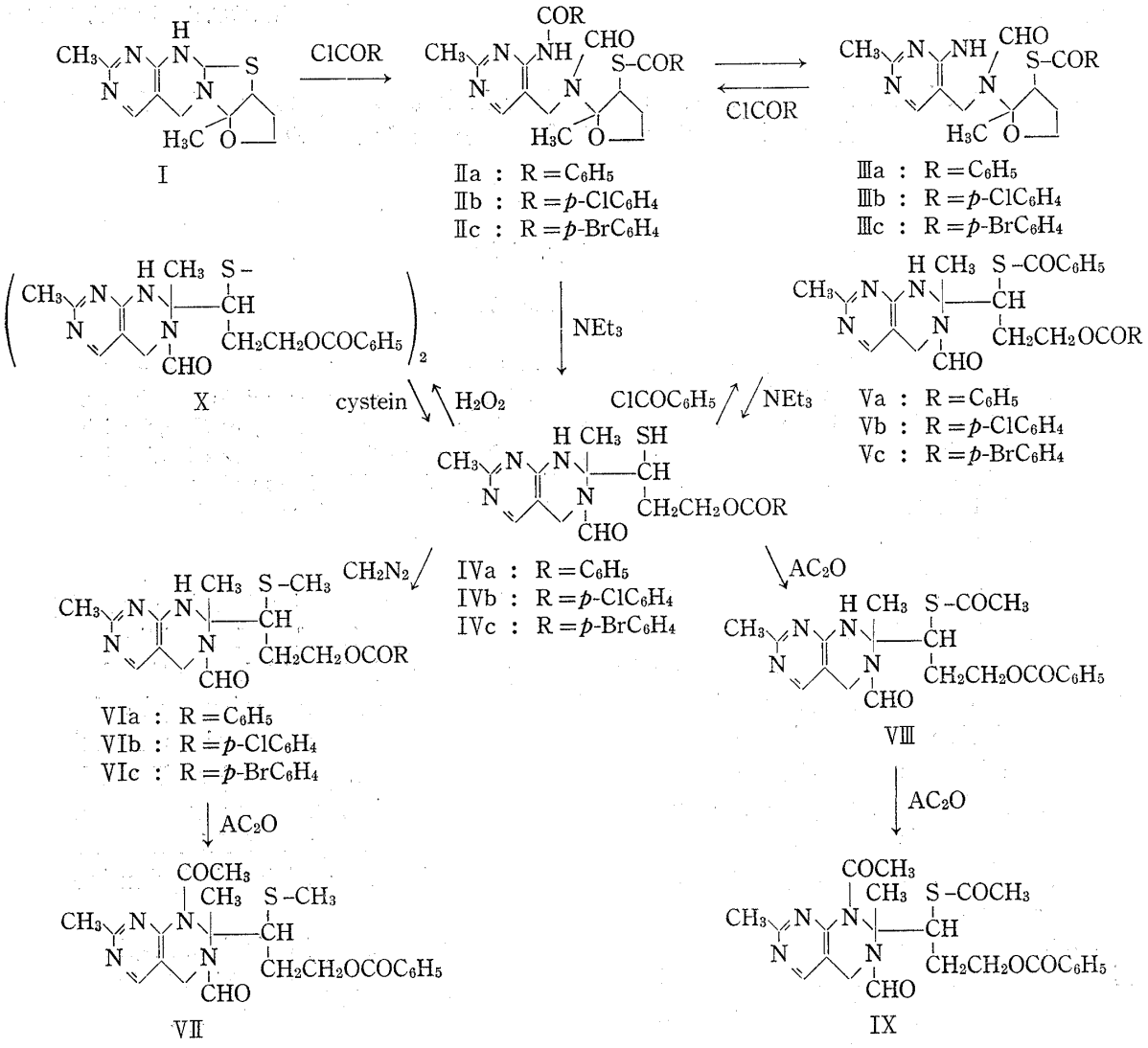


Chart 1

TABLE I. Physicochemical Data for IIa—c and IIIa—c

| Compd. | UV $\lambda_{max}^{EtOH}$ nm (log $\varepsilon$) | IR $\nu_{max}^{Nujol}$ $cm^{-1}$ | NMR ($CDCl_3$, $\tau$) |
|---|---|---|---|
| IIa | 240(3.37), 270(3.32) | 3170(NH), 1691(C=O), 1661(C=O), 1633(C=O) | 8.25 {s, 3H, Furan (Fu)-$C_2$-$CH_3$} 7.38 (s, 3H, Pm-$C_2$-$CH_3$), 5.55 (s, 2H, >-$CH_2$-N), 2.56, 2.11 (m, 10H, 2×$C_6H_5$), 1.70 (s, 1H, Pm-$C_6$-H), 1.40 (s, 1H, N-CHO) |
| IIb | 249(4.46), 271(4.43) | 3250(NH), 1697(C=O), 1668(C=O), | 8.20 (s, 3H, Fu-$C_2$-$CH_3$), 7.33 (s, 3H, Pm-$C_2$-$CH_3$), 5.50 (s, 2H, >-$CH_2$-N), 2.56, 2.11 (m, 8H, 2×$C_6H_4$), 1.65 (s, 1H, Pm-$C_6$-H), 1.33 (s, 1H, N-CHO) |
| IIc | 254(4.49), 271(4.50) | 3260(NH), 1689(C=O), 1672(C=O), 1642(C=O) | 8.21 (s, 3H, Fu-$C_2$-$CH_3$), 7.33 (s, 3H, Pm-$C_2$-$CH_3$), 5.55 (s, 2H, >-$CH_2$-N), 2.40 (m, 8H, 2×$C_6H_4$), 1.66 (s, 1H, Pm-$C_6$-H), 1.36 (s, 1H, NCHO) |
| IIIa | 239(4.25), 271(4.13) | 3307(NH), 3120(NH), 1667(C=O), 1652(C=O) | 8.28 (s, 3H, Fu-$C_2$-$CH_3$), 7.58 (s, 3H, Pm-$C_2$-$CH_3$), 5.58 (s, 2H, >-$CH_2$-N), 3.80 (b, 2H, $NH_2$), 2.50, 2.20 (m, 5H, $C_6H_5$), 1.93 (s, 1H, Pm-$C_6$-H), 1.65 (s, 1H, N-CHO) |
| IIIb | 246(4.21), 255(sh 4.20), 275(4.23) | 3350(NH), 3120(NH), 1666(C=O), 1640(C=O) | 8.28 (s, 3H, Fu-$C_2$-$CH_3$), 7.58 (s, 3H, Pm-$C_2$-$CH_3$), 5.60 (s, 2H, >-$CH_2$-N), 3.76 (b, 2H, $NH_2$), 2.65, 2.18 ($A_2B_2$-q, $J$=10 cps, $C_6H_4$), 1.95 (s, 1H, Pm-$C_6$-H), 1.66 (s, 1H, N-CHO) |
| IIIc | 260(4.26), 275(4.29) | 3350(NH), 3025(NH), 1665(C=O), 1643(C=O) | 8.26 (s, 3H, Fu-$C_2$-$CH_3$), 7.56 (s, 3H, Pm-$C_2$-$CH_3$), 5.55 (s, 2H, >-$CH_2$-N), 3.78 (b, 2H, $NH_2$), 2.35, 2.28 (m, 4H, $C_6H_4$), 1.90 (s, 1H, Pm-$C_6$-H), 1.63 (s, 1H, N-CHO) |

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latter suggesting a O–$COC_6H_5$ system which is known to absorb in the 1700 $cm^{-1}$ region. The reaction of IVa with benzoyl chloride formed a crystalline benzoate (Va) which readily regenerated IVa on triethylamine treatment. The formula of Va, $C_{26}H_{26}O_4N_4S$, supports that it is an isomer of IIa, while its UV spectrum exhibits maxima at 238 (4.36) and 280 (4.07). The IR spectrum shows absorption bands at 3250 (NH or OH), 1713 (C=O), 1673 (C=O), and 1641 $cm^{-1}$ (C=O) suggesting that the newly substituted $\overset{O}{\overset{\|}{C}}C_6H_5$ group (1673 or 1641 $cm^{-1}$) in Va would be attached to the sulfur-or nitrogen anion. The NMR spectrum in deutero-chloroform exhibits signals at $\tau$ value 1.68 {s, 1H, pyrimidine (Pm)–$C_6$–H}, 3.86 (b, 1H, NH), 4.78, 5.88 (AB-q, 2H, $J$=18 cps, Pm–$C_5$–$CH_2$), 7.63 (s, 3H, Pm–$C_2$–$CH_3$), 8.20 (s, 3H, $CH_3$) as shown in Table II. Notable is the presence of the newly observed N–CHO system as a singlet peak at $\tau$ 1.45. This data suggests a structure for IVa containing N–CHO, O–$COC_6H_5$, a tetrahydropyrimidopyrimidine moiety, NH or SH, and lacking a $COC_6H_5$ system. To prove the presence of a free SH group in IVa the reaction of IVa with excess diazomethane was carried out and a crystalline product (VIa) was obtained.

The analysis of VIa corresponds to formula $C_{20}H_{24}O_3N_4S$, which suggests that methylation of IVa proceeded as expected. The UV spectrum of VIa showing maxima at 232 (4.27) and 285 (3.81) indicates that the ring system of IVa is retained. The NMR spectrum of VIa is similar to that of IVa except for a signal at $\tau$ value 7.83 (s, 3H, $CH_3$) which may be assigned as the newly formed S-methyl group as shown in Table II. Next, the treatment of IVa with excess hydrogen peroxide in dilute aqueous sodium hydroxide solution afforded a product (X, mp 164—168°) which analysed as $C_{28}H_{42}O_6N_8S_2$. The UV and NMR spectrum of X were almost identical to those of IV, as shown in Table II. These data gave strong support to the suggestion that X is the disulfide of IVa, and ready regeneration of IVa by reaction of X with cysteine further showed that IVa has a free SH group. Accordingly, the structure of IVa was established to be 1-(2,7-dimethyl-3-formyl-1,2,3,4-tetrahydropyrimido[4,5-*d*]pyrimidin-2-yl)-3-benzoyloxypropylmercaptane, and Va and X were determined to be the S-benzoate and disulfide of IVa respectively. This is the first example of a thiamine derivative containing a free SH group.

Table II. Physicochemical Data for IVa—c, X and Va—c

| Compd. | UV $\lambda_{max}^{EtOH}$ nm (log $\varepsilon$) | IR $\nu_{max}^{Nujol}$ $cm^{-1}$ | NMR ($CDCl_3$, $\tau$) |
|---|---|---|---|
| IVa | 232(4.26), 283(3.82) | 3280(NH), 1730(C=O), 1650(C=O), | 8.05 (s, 2-$CH_3$), 7.46 (s, 7-$CH_3$), 6.18, 4.38 (AB-q, $J$= 18 cps, 4-$CH_2$), 2.80, 2.51 (m, $C_6H_5$), 1.80 (s, 5-H), 1.05 (s, 3-CHO), (in $d_5$-pyridine) |
| IVb | 240(4.40), 284(3.82) | 3280(NH), 1705(C=O), 1649(C=O) | 8.35 (s, 2-$CH_3$), 7.78 (s, 7-$CH_3$), 6.13, 5.70 (AB-q, $J$= 18 cps, 4-$CH_2$), 2.53, 2.50 (m, $C_6H_4$), 1.93 (s, 5-H), 1.51 (s, 3-CHO) |
| IVc | 244(4.41), 285(3.80) | 3325(NH), 1711(C=O), 1646(C=O) | 8.40 (s, 2-$CH_3$), 7.38 (s, 7-$CH_3$), 5.61 (s, 4-$CH_2$), 2.36, 2.15 (m, $C_6H_4$), 1.66 (s, 5-H), 1.48 (s, 3-CHO) |
| X | 233(4.45), 285(4.06) | 3220(NH), 1720(C=O), 1675(C=O) | 8.25 (s, 2-$CH_3$), 7.60 (s, 7-$CH_3$), 5.88, 4.78 (AB-q, $J$= 18 cps, 4-$CH_2$), 4.15 (1-H), 2.01 (s, 5-H), 1.43 (s, 3-CHO) |
| Va | 238(4.37), 280(4.07) | 1713(C=O), 1673(C=O), 1641(C=O) | 8.20 (s, 2-$CH_3$), 7.60 (s, 7-$CH_3$), 5.88, 4.78 (AB-q, $J$= 18 cps, 4-$CH_2$), 2.53, 2.15 (m, 2×$C_6H_5$), 1.88 (s, 5-H), 1.45 (s, 3-CHO) |
| Vb | 242(3.43), 279(3.00) | 1718(C=O), 1670(C=O), 1635(C=O) | 8.15 (s, 2-$CH_3$), 7.53 (s, 7-$CH_3$), 5.90, 4.76 (AB-q, $J$= 17 cps, 4-$CH_2$), 2.61, 2.21 (m, $C_6H_5$, $C_6H_4$), 1.88 (s, 5-H), 1.50 (s, 3-CHO) |
| Vc | 236(4.36), 279(4.24) | 1720(C=O) 1668(C=O) | 8.16 (s, 2-$CH_3$), 7.58 (s, 7-$CH_3$), 5.90, 4.76 (AB-q, $J$= 17 cps, 4-$CH_2$), 2.33 (m, $C_6H_5$, $C_6H_4$), 1.88 (s, 5-H), 1.46 (s, 3-CHO) |

The acetylation of IVa with acetic anhydride gave S-acetate (VIII) under usual reaction conditions, and the exhaustive acetylation of VIII afforded N,S-diacetate (IX) from which

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VIII was easily regenerated by reaction with triethylamine, while the acetylation of VIa gave N-acetate (VII) in fair yield. To investigate in detail the reaction behaviour of IIb and IIc compared with that of IIa, the reactions of IIb and IIc with triethylamine were carried out under similar conditions to those used for formation of IVa; the analogues IVb and IVc were obtained, but in unexpectedly lower yield than IVa. Methylation of IVb and IVc with diazomethane afforded S-methyl analogues (VIb, VIc) of IVa as crystalline products, and the S-benzoylderivatives (Vb and Vc) of IVb and IVc were easily obtained by reaction with benzoyl chloride.

The structures of these compounds were elucidated from their elemental analysis (see Experimental), UV, IR, and NMR spectral data (Tables II and III).

TABLE III. Physicochemical Data for VIa—c and VII

| Compd. | UV $\lambda_{max}^{EtOH}$ nm (log $\varepsilon$) | IR $\nu_{max}^{Nujol}$ $cm^{-1}$ | NMR ($CDCl_3$, $\tau$) |
|---|---|---|---|
| VIa | 232(4.27), 285(3.81) | 3240(NH), 1710(C=O) | 8.21 (s, 2-$CH_3$), 7.83 (s, S-$CH_3$), 7.60 (s, 7-$CH_3$), 6.08, 4.75 (AB-q, $J$=17 cps, 4-$CH_2$), 4.13 (b, 1-H), 1.96 (s, 5-H), 1.36 (s, 3-CHO) |
| VIb | 242(4.33), 285(3.72) | 3200(NH), 1707(C=O) | 8.23 (s, 2-$CH_3$), 7.86 (s, S-$CH_3$), 7.58 (s, 7-$CH_3$), 6.06, 4.71 (AB-q, $J$=17 cps, 4-$CH_2$), 4.28 (b, 1-H), 1.90 (s, 5-H), 1.36 (s, 3-CHO) |
| VIc | 245(4.37), 285(3.77) | 3240(NH), 1720(C=O), 1650(C=O) | 8.23 (s, 2-$CH_3$), 7.86 (s, S-$CH_3$), 7.58 (s, 7-$CH_3$), 6.10, 4.73 (AB-q, $J$=18 cps, 4-$CH_2$), 4.21 (b, 1-H), 1.91 (s, 5-H), 1.36 (s, 3-CHO) |
| VII | 230(3.89), 284(3.58) | 1710(C=O), 1668(C=O) | 7.86 (s, 2-$CH_3$), 7.83 (s, S-$CH_3$), 7.58 (s, N-$COCH_3$), 7.48 (s, 7-$CH_3$), 5.90, 4.70 (AB-q, $J$=18 cps, 4-$CH_2$), 2.48, 2.71 (m, $C_6H_5$), 1.60 (s, 5-H), 1.31 (s, 3-CHO) |

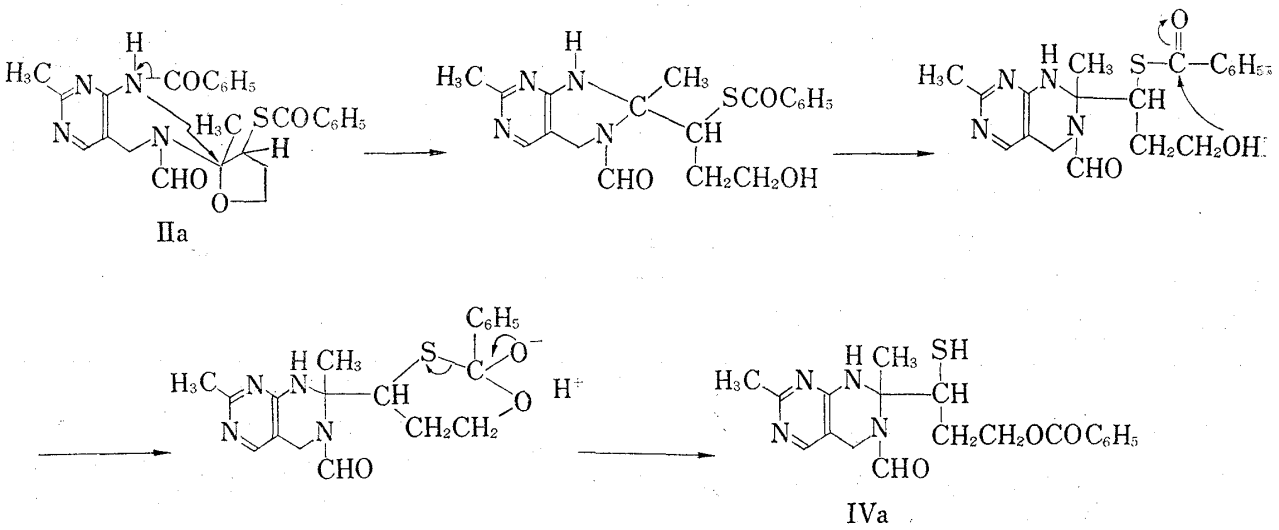

Chart 2

The reaction mechanisms of the formation of IV might be proposed as shown in Chart 2. Since IVa is not produced by triethylamine treatment of IIIa, it may be postulated that the debenzoylation of N–$COC_6H_5$ of IIa under basis conditions promotes this unusual reaction process. In the first step of the reaction, debenzoylation of Pm–$C_4$–$NHCOC_6H_5$ system of IIa might occur, followed by nucleophilic attack of nitrogen anion of Pm–$C_4$–$\bar{N}H$ at the carbon atom adjacent to the oxygen atom of the furan ring to form a pyrimidopyrimidine moiety, and ring cleavage of the furan ring system would produce a intermediate having a $-CH_2CH_2-\overset{O^-}{\underset{|}{O}}-\overset{|}{C}$ system. The newly formed intermediate would not be very stable, so rearrangement of benzoyl group from the sulfur atom to the oxygen atom might easily occur to give IVa as the final stable product.

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The lower yields of IVb and IVc than that of IVa might be due to the stability of these intermediates. The inductive effects of the Cl and Br substituents have presumably little influence on the reactivities of these compounds.

## Experimental

All melting points were determined in capillaries and are uncorrected. NMR spectra were taken on a Varian Associates A-60 spectrometer in $CDCl_3$ or $d_5$-pyridine solution with tetramethylsilane (TMS) as an internal standard. UV spectra were taken on a Hitachi EPS-3 spectrophotometer in 99% EtOH. IR spectra were taken in nujol mull on a Japan Spectroscopic Company IR-S spectrophotometer using a NaCl prism.

**N-(2-Methyl-4-*p*-substitutedbenzamidopyrimidin-5-yl)methyl-N-(2-methyl-3-*p*-substitutedbenzoylthiotetrahydrofuran-2-yl)formamide (IIb, c)**——General Procedure: To a suspension of 10 mmole of I and 25 mmole of $NaHCO_3$ in 100 ml of acetone was added 25 mmole of *p*-substituted benzoyl chloride at 1—5° during 0.5 hr, and the mixture was stirred for 1 hr at room temperature. Acetone was removed *in vacuo* at 40°. The residue 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 purified by $SiO_2$–acetone column chromatography and recrystallized from acetone.

N-(2-Methyl-4-*p*-chlorobenzamidopyrimidin-5-yl)methyl-N-(2-methyl-3-*p*-chlorobenzoylthiotetrahydrofuran-2-yl)-formamide (IIb), yield 1.56 g (28%), colorless crystals, mp 166—167°. *Anal.* Calcd. for $C_{26}H_{24}O_4N_4SCl_2$: C, 55.82; H, 4.32; N, 10.01; S, 5.73; Cl, 12.67. Found: C, 55.93; H, 4.43; N, 9.90; S, 5.91; Cl, 12.74.

N-(2-Methyl-4-*p*-bromobenzamidopyrimidin-5-yl)methyl-N-(2-methyl-3-*p*-bromobenzoylthiotetrahydrofuran-2-yl)formamide (IIc), yield 2.55 g (38%), colorless crystals, mp 180—182°. *Anal.* Calcd. for $C_{26}H_{24}O_4N_4SBr_2$: C, 48.17; H, 3.70; O, 9.87; N, 8.64; S, 4.94; Br, 24.65. Found: C, 48.37; H, 3.95; O, 9.57; N, 8.52; S, 4.83; Br, 24.56.

**N-(2-Methyl-4-aminopyrimidin-5-yl)methyl-N-(2-methyl-3-*p*-substitutedbenzoylthiotetrahydrofuran-2-yl)formamide (IIIb—c)**——General Procedure: To a suspension of 1 mmole of IIb—c in 30 ml of EtOH was added 5 ml of 50% EtOH–HCl under ice cooling to give a clear solution. The solution was stirred for 7 hr at room temperature. After allowing to stand overnight at 0°, the ethanol was concentrated *in vacuo* at 40°, the residue was dissolved in $H_2O$, neutralized with $NaHCO_3$, and extracted with $CHCl_3$. The $CHCl_3$ extract was washed, dried, and evaporated. The residual crystals were washed with ether, filtered, and recrystallized from acetone.

N-(2-Methyl-4-aminopyrimidin-5-yl)methyl-N-(2-methyl-3-*p*-chlorobenzoylthiotetrahydrofuran-2-yl)-formamide (IIIb), yield 580 mg (4.6%), colorless crystals, mp 178—182°. *Anal.* Calcd. for $C_{19}H_{20}O_3N_4SCl$: C, 54.35; H, 4.80; O, 11.43; N, 13.34; S, 7.64; Cl, 8.44. Found: C, 54.18; H, 4.80; O, 11.22; N, 13.08; S, 7.83; Cl, 8.71.

N-(2-Methyl-4-aminopyrimidin-5-yl)methyl-N-(2-methyl-3-*p*-bromobenzoylthiotetrahydrofuran-2-yl)-formamide (IIIc), yield 100 mg (3.5%), colorless crystals, mp 173—176°. *Anal.* Calcd. for $C_{19}H_{20}O_3N_4SBr$: C, 49.04; H, 4.54; O, 10.31; N, 12.04; S, 6.87; Br, 17.17. Found: C, 49.22; H, 4.59; O, 10.04; N, 12.08; S, 7.16; Br, 17.39.

**Benzoylation of IIIa**——To a suspension of 150 mg of IIIa and 65 mg of $NaHCO_3$ in 5 ml of pyridine (dried over KOH) was added 109 mg of benzoyl chloride under ice cooling. After the mixture had been stirred at room temperature for 6.5 hr, pyridine was removed *in vacuo* at 40°. 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 acetone to give 40 mg (22%) of IIa, mp 132—134°, which was identified with an authentic sample by IR spectra comparison.

**1-(2,7-Dimethyl-3-formyl-1,2,3,4-tetrahydropyrimido[4,5-*d*]pyrimidin-5-yl)-3-benzoyl (and *p*-substituted benzoyl)propylmercaptane (IVa, b, c)**——General Procedure: To a suspension of 5 mmole of II in 100 ml of 50% MeOH–$H_2O$ was added 10 mmole of triethylamine under ice cooling. The solution was stirred at room temperature for 5 hr. After allowing to stand overnight, the reaction mixture was evaporated *in vacuo* at 40° and the residue was extracted with $CHCl_3$. The $CHCl_3$ extract was washed with $H_2O$ successively, dried over anhyd. $Na_2SO_4$, and evaporated. The residual crystals were washed with acetone and filtered. The filtered crystals were purified by recrystallization from acetone.

1-(2,7-Dimethyl-3-formyl-1,2,3,4-tetrahydropyrimido[4,5-*d*]pyrimidin-5-yl)-3-benzoylpropylmercaptane (IVa), yield 1.66 g (43%), colorless crystals, mp 193—195°. *Anal.* Calcd. for $C_{19}H_{22}O_3N_4S$: C, 59.09; H, 5.74; O, 12.42; N, 14.50; S, 8.30. Found: C, 59.16; H, 5.76; O, 12.43; N, 14.30; S, 8.64.

1-(2,7-Dimethyl-3-formyl-1,2,3,4-tetrahydropyrimido[4,5-*d*]pyrimidin-5-yl)-3-*p*-chlorobenzoylpropylmercaptane (IVb), yield 1.9 g (29%), colorless crystals, mp 164—166°. *Anal.* Calcd. for $C_{19}H_{21}O_3N_4SCl$: C, 54.21; H, 5.02; O, 11.18; N, 13.31; S, 7.61; Cl, 8.42. Found: C, 53.98; H, 4.93; O, 11.11; S, 13.18; S, 7.61; Cl, 8.34.

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1-(2,7-Dimethyl-3-formyl-1,2,3,4-tetrahydropyrimido[4,5-*d*]pyrimidin-5-yl)-3-*p*-bromobenzoylpropylmercaptane (IVc), yield 1.53 g (22%), colorless prisms, mp 162—164°. *Anal.* Calcd. for $C_{19}H_{21}O_3N_4SBr$: C, 49.04; H, 4.54; O, 10.31; N, 12.03; S, 6.89; Br, 17.17. Found: C, 49.26; H, 4.27; O, 10.18; N, 12.18; S, 6.72; Br, 17.24.

**2,7-Dimethyl-2-{1-benzoylthio-3-benzoyl (and *p*-substituted benzoyl)oxy} propyl-1,2,3,4-tetrahydropyrimido[4,5-*d*]pyrimidine-3-carbaldehyde (Va, b, c)**——General Procedure: To a suspension of 1 mmole of IVa in 10 ml of pyridine (dried over KOH) was added 1.2 mmole of benzoyl chloride under ice cooling. The mixture was stirred at room temperature for 5 hr, then pyridine was removed *in vacuo* at 40°. 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 V which was purified by recrystallization from acetone.

2,7-Dimethyl-2-(1-benzoylthio-3-benzoyloxy)propyl-1,2,3,4-tetrahydropyrimido[4,5-*d*]pyrimidine-3-carbaldehyde (Va), yield 458 mg (94%), colorless crystals, mp 218—219°. *Anal.* Calcd. for $C_{26}H_{26}O_4N_4S$: C, 63.66; H, 5.34; O, 13.06; N, 11.42; S, 6.53. Found: C, 63.80; H, 5.25; O, 12.19; S, 6.95.

2,7-Dimethyl-2-(1-benzoylthio-3-*p*-chlorobenzoyloxy)propyl-1,2,3,4-tetrahydropyrimido[4,5-*d*]pyrimidine-3-carbaldehyde (Vb), yield 183 mg (69.5%), colorless crystals, mp 143—148°. *Anal.* Calcd. for $C_{26}H_{25}O_4N_4SCl$: C, 59.48; H, 4.80; O, 12.19; N, 10.67; S, 6.07; Cl, 6.75. Found: C, 59.33; H, 5.41; O, 13.00; N, 10.77; S, 6.08; Cl, 6.99.

2,7-Dimethyl-2-(1-benzoylthio-3-*p*-bromobenzoyloxy)propyl-1,2,3,4-tetrahydropyrimido[4,5-*d*]pyrimidine-3-carbaldehyde (Vc), yield 43 mg (22%) amorphous. *Anal.* Calcd. for $C_{26}H_{25}O_4N_4SBr$: C, 54.83; H, 4.42; O, 11.23; N, 9.59; S, 5.63. Found: C, 54.60; H, 4.24; O, 11.50; N, 9.59; S, 5.67.

**Treatment of Va with $NEt_3$**——To a suspension of 40 mg (0.08 mmole) of Va in 3 ml of 30% MeOH was added 27.3 mg (0.27 mmole) of $NEt_3$ and the mixture was stirred at room temperature for 6 hr. After allowing to stand overnight at 0°, the reaction mixture was evaporated *in vacuo*, and the residue was extracted with $CHCl_3$. The $CHCl_3$ extract was dried over anhyd. $Na_2SO_4$, evaporated, and the residue was treated with acetone to give 4 mg (12.5%) of IVa. The IR spectrum of this product was identical with that of IVa obtained above.

**2,7-Dimethyl-2-{3-benzoyl (and *p*-substitutedbenzoyl)oxy-1-methylthio}propyl-1,2,3,4-tetrahydropyrimido[4,5-*d*]pyrimidine-3-carbaldehyde (VIa, b, c)**——General Procedure: To a solution of 1 mmole of IV in 40 ml of tetrahydrofuran (THF) was added excess $CH_2N_2$ in ether. The solution was stirred at room temperature for 5 hr, then THF was removed *in vacuo* at 30° and the residue was extracted with $CHCl_3$. The $CHCl_3$ extract was washed with $H_2O$, dried over anhyd. $Na_2SO_4$, and evaporated. The residual product was purified by recrystallization from ether–acetone.

2,7-Dimethyl-2-(3-benzoyloxy-1-methylthio)propyl-1,2,3,4-tetrahydropyrimido[4,5-*d*]pyrimidine-3-carbaldehyde (VIa), yield 342 mg (86%), colorless prisms, mp 166—168°. *Anal.* Calcd. for $C_{20}H_{24}O_3N_4S$: C, 59.99; H, 6.04; N, 13.99; S, 7.99. Found: C, 59.99; H, 6.04; N, 13.72; S, 8.00.

2,7-Dimethyl-2-(3-*p*-chlorobenzoyloxy-1-methylthio)propyl-1,2,3,4-tetrahydropyrimido[4,5-*d*]pyrimidine-3-carbaldehyde (VIb), yield 313 mg (72%), colorless prisms, mp 171—174°. *Anal.* Calcd. for $C_{20}H_{23}O_3N_4SCl$: C, 55.23; H, 5.32; N, 12.88; S, 7.37; Cl, 8.15. Found: C, 55.02; H, 5.57; N, 12.59; S, 7.64; Cl, 8.47.

2,7-Dimethyl-2-(3-*p*-bromobenzoyloxy-1-methylthio)propyl-1,2,3,4-tetrahydropyrimido[4,5-*d*]pyrimidine-3-carbaldehyde (VIc), yield 210 mg (44%), colorless crystals, mp 98—110°. *Anal.* Calcd. for $C_{20}H_{23}O_3N_4SBr$: C, 50.11; H, 4.83; N, 11.68; S, 6.69. Found: C, 50.06; H, 5.00; N, 11.85; S, 6.35.

**1-Acetyl-2,7-dimethyl-2-(3-benzoyloxy-1-methylthiopropyl-1,2,3,4-tetrahydropyrimido[4,5-*d*]pyrimidine-3-carbaldehyde (VII)**——A solution of 200mg (0.5 mmole) of VIa in 5 g of $Ac_2O$ was refluxed for 6 hr. The solution was allowed to stand overnight at room temperature, then the solution was concentrated *in vacuo* at 60° and the residue was extracted with $CHCl_3$. The $CHCl_3$ extract was washed with 10% $NaHCO_3$ and $H_2O$ successively, dried over anhyd. $Na_2SO_4$, and evaporated. Silica gel column chromatography of the residue with AcOEt gave 30 mg (27%) of VII. Recrystallization from ether gave colorless crystals, mp 158—159°. *Anal.* Calcd. for $C_{22}H_{26}O_4N_4S$: C, 59.71; H, 5.92; O, 14.46; N, 12.66. Found: C, 60.07; H, 5.90; O, 14.38; N, 12.61.

**2,7-Dimethyl-2-(3-benzoyloxy-1-acetylthiopropyl-1,2,3,4-tetrahydropyrimido[4,5-*d*]pyrimidine-3-carbaldehyde (VIII)**——To a suspension of 386 mg (1 mmole) of IVa and 184 mg (2.2 mmole) of $NaHCO_3$ in 10 ml of pyridine (dried over KOH) was added 224 mg (2.2 mmole) of $Ac_2O$ and the mixture was stirred at room temperature for 2 hr. The reaction mixture was concentrated *in vacuo* at 40°, and the residue was extracted with $CHCl_3$. The $CHCl_3$ extract was washed with $H_2O$, dried over anhyd. $Na_2SO_4$, and evaporated. The residual oil was crystallized from ether–acetone to yield 383 mg (90%) of VIII as colorless crystals. Recrystallization from acetone gave colorless prisms, mp 170—171°. *Anal.* Calcd. for $C_{21}H_{24}O_4N_4S\cdot(CH_3)_2CO$: C, 59.25; H, 6.22; N, 11.52; S, 6.57. Found: C, 59.02; H, 6.18; N, 11.52; S, 6.83. UV $\lambda_{max}^{EtOH}$ mμ(log ε): 231, 281 (shoulder) (4.53, 3.95). IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 3200 (NH), 1705, 1632 (C=O). NMR ($CDCl_3$, τ): 8.21 (s, 3H, 2-$CH_3$), 7.66 (s, 3H, S-$COCH_3$), 7.60 (s, 3H, 7-$CH_3$), 5.98, 4.80 (AB-q, $J$=18, 4-$CH_2$), 2.51 (m, 5H, $C_6H_5$), 1.88 (s, 1H, Pm-$C_2$-H-), 1.46 (s, 1H, N-CHO).

**1-Acetyl-2,7-dimethyl-2-(3-benzoyloxy-1-acetylthio)propyl-1,2,3,4-tetrahydropyrimido[4,5-*d*]pyrimidine-3-carbaldehyde (IX)**——A solution of 214 mg (0.5 mmole) of VIII in 5 g of $Ac_2O$ was refluxed for 7 hr. After

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allowing to stand overnight at room temperature, $Ac_2O$ was removed *in vacuo* at 60° and the residue was extracted with $CHCl_3$. The $CHCl_3$ extract was washed with 10% $NaHCO_3$ and $H_2O$ successively, dried over anhyd. $Na_2SO_4$, and evaporated. The residue was chromatographed on silica gel with acetone to give 54 mg (36%) of IX. Recrystallization from ether–acetone gave colorless prisms, mp 174—175°. *Anal.* Calcd. for $C_{23}H_{26}O_5N_4S$: C, 58.70; H, 5.56; O, 17.00; N, 11.90; S, 6.81. Found: C, 58.69; H, 5.72; O, 17.52; N, 12.11; S, 7.07. UV $\lambda_{max}^{EtOH}$ mμ(log ε): 229, 283 (4.28, 3.92). IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 1709, 1661 (C=O). NMR ($CDCl_3$, τ): 7.86 (s, 3H, 2-$CH_3$), 7.70 (s, 3H, N–$COCH_3$), 7.63 (s, 3H, S–$COCH_3$), 7.56 (s, 3H, 7-$CH_3$), 5.95, 4.71 (AB-q, $J$=18 cps, 4-$CH_2$), 2.51, 2.48 (m, 5H, $C_6H_5$), 1.60 (s, 1H, Pm-$C_6$-H), 1.41 (s, 1H, N–CHO).

**1-(2,7-Dimethyl-3-formyl-1,2,3,4-tetrahydropyrimido[4,5-*d*]pyrimidin-2-yl)-3-benzoyloxypropyldisulfide (X)**——To a solution of 386 mg (1 mmole) of IVa in 10 ml of 60% MeOH–$H_2O$ and 2 ml of 1% NaOH (0.5 mmole) was added 58 mg (0.5 mmole) of 30%-$H_2O_2$ under ice-cooling with stirring. The solution was stirred under ice-cooling for 2.5 hr, then the reaction mixture was concentrated *in vacuo* and the residue was extracted with $CHCl_3$. The $CHCl_3$ extract was washed with $H_2O$ successively, dried over anhyd. $Na_2SO_4$, and evaporated. The residue was treated with acetone to give 279 mg (72%) of X. Recrystallization from acetone gave colorless prisms, mp 154—168°. *Anal.* Calcd. for $C_{28}H_{42}O_6N_8S_2 \cdot 1/2H_2O$; mol. wt., 815.9: C, 55.93; H, 5.81; N, 13.73; S, 7.86. Found; mol. wt., 741 (in Py): C, 55.85; H, 5.89; N, 14.03; S, 8.10.

**Reduction of X with Cystein (IVa)**——To a solution of 39 mg (0.05 mmole) of X in 20 ml of MeOH was added 4 ml of 0.3% cystein ($H_2O$ solution) and the solution was stirred at room temperature for 3.5 hr. After removal of the solvent *in vacuo*, the residual crystals were washed with 150 ml of $H_2O$ successively, then with acetone to give 5 mg (12.8%) of IVa, identified with IVa obtained above by IR spectra comparison.

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