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Studies on Pyrimidine Derivatives and Related Compounds. LXXX.[1] Unusual Reactions of Thiamine Free Base with Electrophilic Reagents. (2)[2]

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The reaction of thiamine free base (I) with isocyanate derivatives in polar solvent such as dimethylformamide afforded 2-(7-methyl-3,4-dihydropyrimido[4,5-*d*]pyrimidin-3-yl)-2-methyltetrahydrofuran-3-yl alkyl(aryl)carbamthiolate (V), which then reacted with another isocyanate molecule to give N-carbamoylthiamine free base (II). The reaction mechanism is discussed kinetically. The reaction of I with isocyanate derivatives in less polar solvent such as chloroform afforded only II-analogues. The reaction of II with N,N-disubstituted carbamoylchlorides afforded 2-[N-formyl-N-(2-methyl-4-aminopyrimidin-5-yl)methyl]amino-2-methyltetrahydrofuran-3-yl disubstituted carbamthiolates (VIIa—c).

In previous papers[4,5] we reported that reaction of thiamine free base (I) with ethyl pyrocarbonate, benzoyl chloride, and phenylisocyanate in dimethylformamide (DMF) gave the 1:2-addition product (IV), the dibenzoate (IIIa) and N-phenylcarbamoylthiamine free base (IIc) respectively. This paper deals with the reaction of I with some other electrophiles; isocyanates and chlorocarbamates. It has become apparent that in the reaction of I with phenylisocyanate or other isocyanate derivatives in a polar solvent such as DMF, an adduct (V) is initially formed between the S-anion generated by ring opening of the thiazolidine moiety and the isocyanate molecule, the ring being then re-closed by the action of another isocyanate molecule to give finally IIc or its analogues. Thus the reaction mechanism is, on the whole, similar to that with ethyl pyrocarbonate.

The reaction of I with methylisocyanate was carried out in DMF solution to give two isomers (Va and IIa) as colourless crystals. Isomer IIa was confirmed as an analogue of IIc, *i.e.* N-methylcarbamoylthiamine free base, on the basis of its elemental analysis, infrared (IR), ultraviolet (UV), and nuclear magnetic resonance (NMR) spectral data (see Experimental). The molecular formula of Va, $C_{14}H_{19}O_2N_5S$, corresponded to that of a 1:1 adduct of I and methylisocyanate, showing that Va is an isomer of IIa.

The UV spectrum of Va has maxima at 229 mμ (log ε 4.93) and 330 (4.97), showing marked bathochromic shift compared with the spectrum of I (245 and 285 mμ). This spectrum would suggest that a dihydropyrimidopyrimidine moiety is formed by dehydrogenation of the tetrahydropyrimidopyrimidine nucleus of I. The IR spectrum shows an absorption band at 1680 (C=O) which might be attributed to S-C=O or N-C=O. The NMR spectrum in deuterochloroform exhibits signals at τ value 1.81 {b, 1H, 2.0, s, 1H, pyrimidine (Pm)-C_6-H}, 5.40 {AB quartet, 2H, Pm-C_5-$C\underline{H}_2$-N, (J=16 cps)}, 7.16 (3H, d, (J=2.5 cps), CH_3), 7.46 (s, Pm-C_2-CH_3) and 8.30 (3H, s, CH_3). It is notable that a doublet peak at τ 7.16 changed to a sharp singlet peak, and a broad peak at τ 1.81 disappeared on treatment with D_2O. Therefore, it is reasonable to conclude that the structure of Va contains an $NHCH_3$ group.

1) Part LXXIX: A. Takamizawa and S. Matsumoto, *Chem. Pharm. Bull.* (Tokyo), **21**, 1300 (1973).
2) A part of this paper was presented at 19th- and 21st-Annual Meeting of the Kinki Branch of the Pharmaceutical Society of Japan at Osaka, November 1969 and 1971.
3) Location: *Fukushima-ku, Osaka, 553, Japan.*
4) A. Takamizawa, I. Makino, and S. Yonezawa, *Chem. Pharm. Bull.* (Tokyo), **21**, 785 (1973).
5) A. Takamizawa, K. Hirai, T. Ishiba, and I. Makino, *Chem. Pharm. Bull.* (Tokyo), **19**, 759 (1971).

The singlet peak at τ 8.45 in the spectrum of I, due to the thiazole (th)-C_4-CH_3,[5] is shifted also to a higher field, τ 8.30, in the spectrum of Va; while proton signals due to the th-C_5-CH_2CH_2-*o*-group are observed as complicated patterns at τ 5.78, 5.91, as in the spectrum of I.[5] These findings suggest that the original tetrahydrofuran ring system of I is retained, and strongly support the structure 2-(7-methyl-3,4-dihydropyrimido[4,5-*d*]pyrimidin-3-yl)-2-methyltetrahydrofuran-3-yl methylcarbamthiolate for Va.

Heating Va in aqueous-alcohol at 50° gave colourless crystals (VI) whose analytical data are consistent with $C_{14}H_{21}O_3N_5S \cdot H_2O$, corresponding to a 1:1 adduct monohydrate of Va and H_2O. The UV spectrum of VI exhibits maxima at 235 mμ (log ε 3.92) and 277 (3.68) showing marked hypsochromic shifts compared with the spectrum of Va so it is evident that hydrolysis of the dihydropyrimidopyrimidine ring of Va must have occurred. The IR spectrum shows an absorption band at 3240 (NH) and carbonyl bands at 1670 and 1638, confirming that the structure of VI contains an S-C=O or N-C=O system. The NMR spectrum of VI in deuterochloroform exhibits signals at τ 1.96 (s, 1H, Pm-C_6-H), 5.65 (s, 2H, Pm-C_5-CH_2-N), 7.53 (s, 3H, Pm-C_2-CH_3), 7.11 (d, 3H, N_4-$\underline{CH}_3$) and 8.31 (s, 3H, th-C_4-CH_3). The latter signal closely resembling that appearing at τ 8.30 in the spectrum of V, and thus providing evidence for a structure of VI containing the tetrahydrofuran ring system. Furthermore, new proton signals are recognized for NH_2 (b) at τ 3.91 and NCHO (S) at τ about 1.70. From these results the structure 2-[N-formyl-N-(2-methyl-4-aminopyrimidin-5-yl)methyl]amino-2-methyltetrahydrofuran-3-yl methylcarbamthiolate can be assigned for VI. We considered it to be of particular interest to confirm the structure of VI by identification with an authentic sample synthesized by a reliable alternative route, also to investigate the reaction of I or II with some carbamoyl chlorides, in connection with the reaction of I with benzoyl chloride and ethyl chlorocarbonate reported in our previous paper.[4] The reaction of I with methyl(triphenylmethyl)carbamoyl chloride was fruitless; however, reaction of IIc with methyl(triphenylmethyl)carbamoyl chloride under the usual reaction conditions afforded a product (VIIc) as colourless crystals with a molecular formula $C_{40}H_{40}O_4N_6S \cdot H_2O$. VIIc was established as the expected 2-[N-formyl-N-(2-methyl-4-aminopyrimidin-5-yl)methyl]-amino-2-methyltetrahydrofuran-3-yl methyl(triphenylmethyl)carbamthiolate (VII) from its UV, IR and NMR spectral data (see Experimental). Treatment of VIIc with 20% HCl–EtOH at 40° gave colourless crystals (VIII) whose analytical data are consistent with $C_{21}H_{26}O_4N_6S$, corresponding to those of the detriphenylmethyl derivative of VIIc as expected. VIII was identified by IR with a sample produced by reaction of VI with phenylisocyanate under the usual conditions.

Accordingly, the structures of Va, VI, VIIc and VIII were confirmed. Reaction of IIc with dimethylcarbamoylchloride or methylbenzylcarbamoylchloride afforded the dimethylcarbamoyl-(VIIa) or methylbenzylcarbamoyl analogue (VIIb), respectively, under the similar reaction condition. The structures of VIIa and VIIb were confirmed by elemental analysis, and UV, IR and NMR spectral data (see Expeimental).

The establishment of the structure of Va prompted us to examine the behaviour of I with some other isocyanates. Reaction of I with ethylisocyanate or phenylisocyanate was carried out under the same conditions as used with methylisocyanate and with almost similar results, two pairs of isomers (II- and V-analogues) were obtained. The structures of N-ethylcarbamoylthiamine free base (IIb), the N-ethylcarbamthiolate derivative (Vb) and the N-phenylcarbamthiolate derivative (Vc) were deduced from their elemental analysis, and IR, UV and NMR spectral data (see Experimental).

In the formation of the V-analogues (Vb—Vc), ethylisocyanate was more reactive than phenylisocyanate; while the reverse was the case in the formation of the N-carbamoylthiamine free bases (IIb or IIc). From these experiments (see Table I), it is evident that the ratio of II/V produced increases largely as the reaction time is increased, and that reaction to II is easier with phenylisocyanate than with ethylisocyanate.

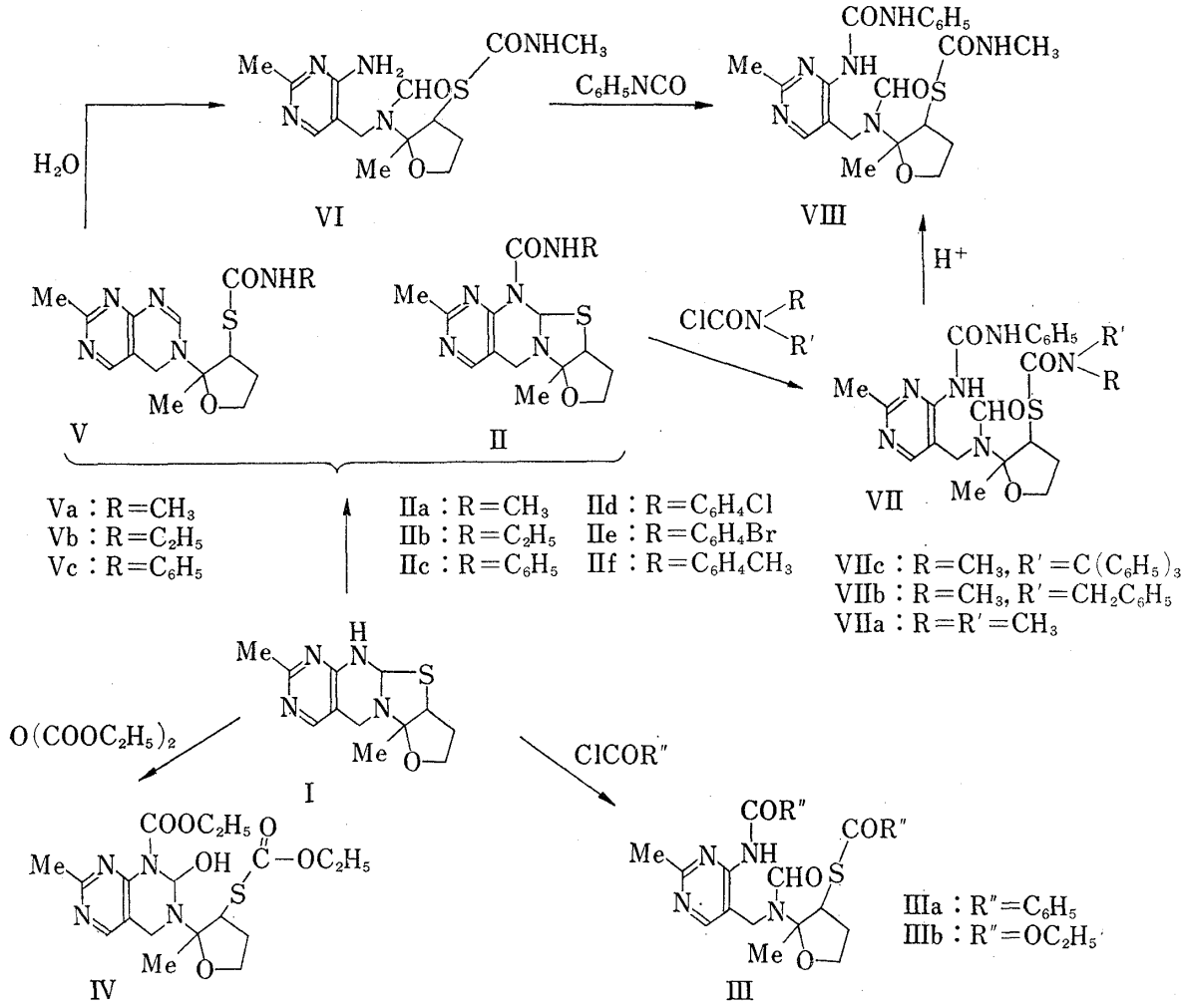
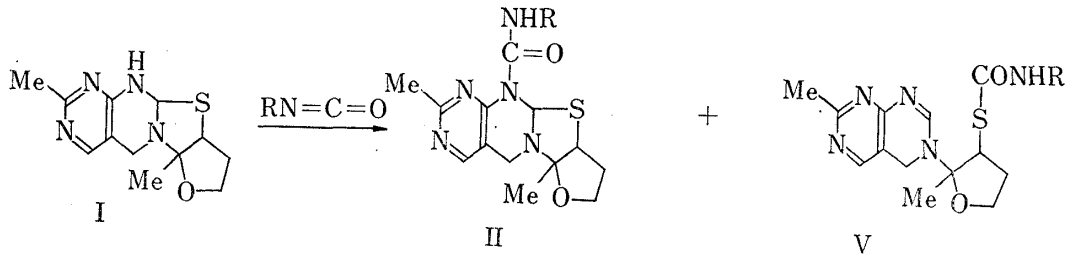


Chart 1

TABLE I. The Product Ratio on the Reactions of I with Isocyanates under the Varied Reaction Time at Room Temperature



R–N=C=O	RNCO eq. mole	Reaction time	II (%)	V (%)	I (%)
C_2H_5–N=C=O	1	20 hr	2.6	16.1	41.6
C_2H_5–N=C=O	1	50 hr	44.7	3.0	40.6
C_2H_5–N=C=O	3	30 min	10.3	21.1	53.2
C_2H_5–N=C=O	3	2 hr	57.2	trace	42.1
C_6H_5–N=C=O	1	10 min	27.0	8.0	53.0
C_6H_5–N=C=O	1	1 hr	65.8	0	30.0

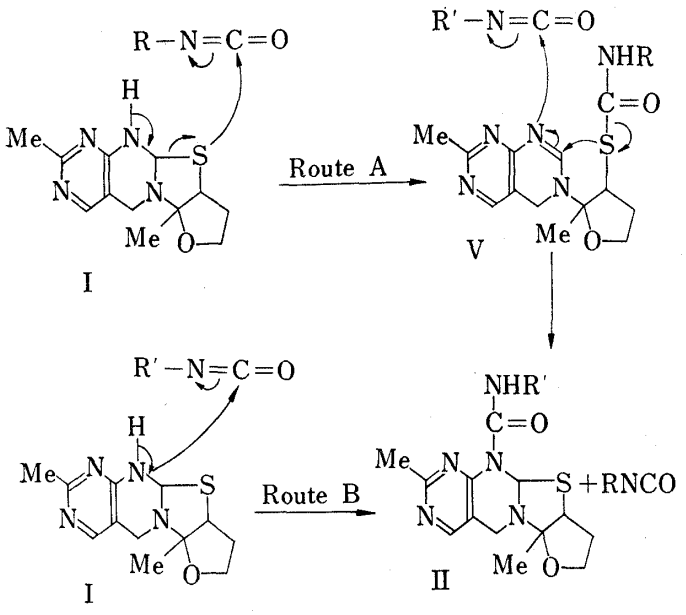


Chart 2

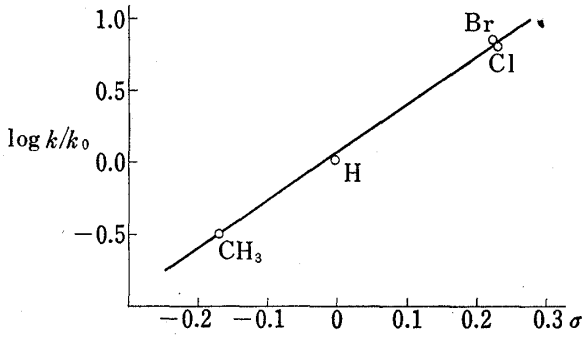


Fig. 1. Plot of log k/k_0 *vs.* Constants for the Reaction of Va with *p*-Substituted Phenylisocyanates

TABLE II. Pseudo First Order Rate Constants in the Reaction of (Va) with *p*-Substituted Phenylisocyanates in N,N-Dimethylformamide Solutions at 40°

Isocyanate	k (sec^{-1})	log k/k_0	σ	ρ average
CH_3-C$_6$H$_4$-NCO	1.1×10^{-6}	−0.50	−0.170	
C$_6$H$_5$-NCO	3.5×10^{-6}	0.00	0.000	
Cl-C$_6$H$_4$-NCO	2.1×10^{-5}	+0.78	0.232	3.35
Br-C$_6$H$_4$-NCO	2.5×10^{-5}	+0.86	0.227	

line and a ρ value of +3.35 as shown in Fig. 1

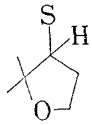
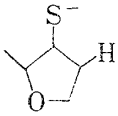
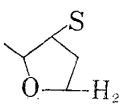
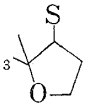
Accordingly, it was considered that two consecutive reactions are involved, as shown in Chart 2; the initial formation of V from the reaction of I with isocyanate, and the subsequent formation of II from V by attack of another isocyanate molecule. The successful conversion of Va to IIb by reaction with ethylisocyanate confirmed this route. We also studied the kinetics of the reaction of Vb with *p*-substituted phenylisocyanates, by measuring the disappearance of the Vb absorption at 331 mμ as a function of time on reaction with a ten-fold excess of isocyanates in DMF solution. Pseudo first order rate constants were obtained by plotting, and the rate constants are listed in Table II. A Hammett plot of log k/k_0 (where k_0 is the pseudo first order rate constant for phenylisocyanate) $\nu_{s,a}$[6] gave a good straight line and the ρ value. From the Hammett $\rho\sigma$ relationship, the key step is seen to be the nucleophilic addition of the Pm-C_4-amino nitrogen to *p*-substituted phenylisocyanate, a result which supports the reaction mechanism proposed above. We expected that the C-S bond of I might be more stable in less polar solvents such as chloroform, so that the reaction of I with isocyanates to form V would be difficult in such solvents. This was found to be true; the reaction between I and isocyanate derivatives in chloroform gave only II-analogues in good yield.

6) D.H. McDaniel and H.C. Brown, *J. Org. Chem.*, **23**, 420 (1958).

Experimantal

Reaction of Thiamine Free Base (I) with MeNCO——To a suspension of 3.96 g of I in 30 ml of dry DMF was added 855 mg of MeNCO at room temperature. Stirring was continued 12 hr then the reaction mixture was allowed to stand overnight. After removal of solvent *in vacuo*, the residue was extracted with $CHCl_3$. The $CHCl_3$ layer was washed with H_2O successively, dried over anhyd. Na_2SO_4 and evaporated. The residual crystals were washed with acetone and collected by filtration. Recrystallization from acetone gave 2-(7-methyl-3,4-dihydropyrimido[4,5-*d*]pyrimidin-3-yl)-2-methyltetrahydrofuran-3-yl methylcarbamthiolate (Va), mp 141—142°, yielding 500 mg, 21.2%. *Anal.* Calcd. for $C_{14}H_{19}O_2N_5S$: C, 52.33; H, 5.95; O, 9.96; N, 21.80; S, 9.92. Found: C, 52.38; H, 5.93; O, 9.94; N, 21.49; S, 10.03. UV λ_{max}^{EtOH} mμ (log ε): 229 (4.93), 330 (4.97). IR ν_{max}^{Nujol} cm^{-1}: 1680 (C=O). NMR ($CDCl_3$) τ: 8.30 (s, 3H, Fu-C_2-CH_3), 7.46 (s, 3H, Pm-C_2-CH_3), 2.30 (s, 1H).

The acetone solution was chromatographed on a silica gel column and eluted with acetone. The isolated crude product was refined by recrystallization from AcOEt to give 2,6a-dimethyl-11-methylcarbamoyl-6a,8,9,9a, 10a, 11-hexahydro-5H-furo[2,3-*h*]thiachromine (IIa), mp 161—162°, yielding 200 mg, 19%. *Anal.* Calcd. for $C_{14}H_{19}O_2N_5S \cdot 1/2H_2O$: C, 50.90; H, 6.06; O, 12.21; N, 21.21; S, 9.69. Found: C, 50.62; H, 6.09; O, 12.43; N, 20.92; S, 9.69.

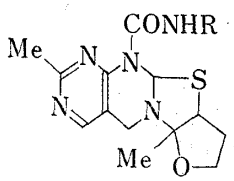
Reaction of I with Ethylisocyanate——a) To a suspension of 2.64 g of I in 30 ml dry DMF, 1.86 g of EtNCO was added at room temperature, then after being stirred for 30 min, the reaction mixture was treated as described above, yielding 0.706 g (21.1%) of 2-(7-methyl-3,4-dihydropyrimido[4,5-*d*]pyrimidin-3-yl)-2-methyltetrahydrofuran-3-yl ethylcarbamthiolate (Vb), mp 138—143° and 0.341 g (10.3%) of 2,6a-dimethyl-11-ethylcarbamoyl-6a,8,9,9a,10a,11-hexahydro-5H-furo[2,3-*h*]thiachromine (IIb), mp 122—123°. IVb: *Anal.* Calcd. for $C_{15}H_{21}O_2N_5S$: C, 53.72; H, 6.32; O, 9.54; N, 20.89; S, 9.54. Found: C, 53.45; H, 6.16; O, 9.51; N, 20.76; S, 9.62. UV λ_{max}^{EtOH} mμ (log ε): 229 (3.93), 330 (3.95). IR ν_{max}^{Nujol} cm^{-1}: 1676 (C=O). NMR ($CDCl_3$) τ (J=Hz): 2.00 (s, 1H,), 2.31 (s, 1H, Pm-C_6-H), 5.42 (ABq, 2H, -CH_2-N, J=14), 5.70, 5.81, 5.95, 6.01, 6.08 (m, 3H, and ), 8.88 (t, 3H, S-$COCH_2CH_3$, J=7). IIb: *Anal.* Calcd. for $C_{15}H_{21}O_2N_5S$: C, 53.72; H, 6.22; O, 9.54; N, 20.89; S, 9.54. Found: C, 53.90; H, 6.31; O, 9.31; N, 21.08; S, 9.73. UV λ_{max}^{EtOH} mμ (log ε): 240 (3.86), 281.5 (3.92). IR ν_{max}^{Nujol} cm^{-1}: 1680 (C=O). NMR ($CDCl_3$) τ (J=Hz): 1.56 (b, 1H, CONHEt), 1.81, 1.91 (s, 1H, Pm-C_6-H), 3.4, 3.50 (s, 1H, ), 5.95 (s, 2H, Pm-CH_2-N), 6.11 (m, 2H, ), 6.55, 6.33 (q, 2H, N-CH_2-CH_3, J=7), 7.43 (s, 3H, Pm-C_2-CH_3), 7.83, 8.10, 8.50 (m, 2H, ), 8.48 (s, 3H, ), 8.78 (t, 3H, S-CoNHCH$_2$C$\underline{H}_3$, J=7).

b) A DMF solution of 2.64 g of I and 1.86 g of EtNCO was stirred for 2 hr at room temperature, then the reaction mixture was treated as described for the formation of Va and IIa, yielding trace of Vb and 1.3 g (42.1%) of IIb which was identified with IIb obtained above by comparison of IR spectra.

Reaction of I with Phenylisocyanate——a) To a suspension of 2.64 g of I in 30 ml dry DMF, 1.19 g of PhNCO was added under ice-cooling. After being stirred for 10 min at 2—3°, the reaction mixture was treated as described for the formation of Va and IIa, yielding 0.3 g (8%) of 2-(7-methyl-3,4-dihydropyrimido[3,4-*d*]-pyrimidin-3-yl)-2-methyltetrahydrofuran-3-yl phenylcarbamthiolate (Vc), mp 164—168° (decomp.) and 1 g (27%) of IIc, mp 175°. Vc: *Anal.* Calcd. for $C_{19}H_{21}O_2N_5S$: C, 59.52; H, 5.52; O, 8.35; N, 18.29; S, 8.35. Found: C, 59.65; H, 5.65; O, 8.74; N, 18.10; S, 8.40. UV λ_{max}^{EtOH} mμ (log ε): 236 (4.19), 250 (4.26), 330 (3.90). IR ν_{max}^{Nujol} cm^{-1}: 1725 (C=O). NMR ($CDCl_3$) τ (J=Hz): −2.50 (b, 1H, -N$\underline{H}$-COC_6H_5), 1.80 (s, 1H, Pm-C_6-H), 2.00 (s, 1H, ), 5.83 (s, 2H, Pm-C_5CH_2-N), 7.50 (s, 3H, Pm-C_2-CH_3), 8.41 (s, 3H, CH_3>-O-).

General Procedure for Prolonged Reaction of I with *p*-Substituted Phenylisocyanate——To a suspension of I (0.01 mole) in 30 ml of DMF, RNCO (0.01 mole) was added at room temperature. After being stirred for 3 hr, the reaction mixture was treated as described for the formation of IIc and Vc. Only II-analogs were obtained. Results are summerized in Tables III and IV.

TABLE III.



No.	R	mp (°C)	Yield	Formula	Analysis					
					Calcd.			Found		
					C	H	N	C	H	N
IIc	C_6H_5	175	65.8							
IId	$C_6H_4Cl(p)$	188—192(decomp.)	72	$C_{19}H_{20}N_5O_2SCl$	54.60	4.82	16.75	54.36	4.96	16.87
IIe	$C_6H_4Br(p)$	182—185(decomp.)	65	$C_{19}H_{20}O_2N_5SBr$	49.35	4.36	15.14	49.74	4.61	15.17
IIf	$C_6H_4CH_3(p)$	185—188(decomp.)	71.3	$C_{20}H_{23}O_2N_5S$	60.44	5.83	17.62	60.54	5.99	17.57

TABLE IV. The Physicochemical Data of IIc and Its *p*-Substituted Analogous

Compound	UV λ_{max}^{EtOH} mμ (log ε)	IR ν_{max}^{Nujol} cm^{-1}	NMR ($CDCl_3$) (τ)
IIc	230, 251, 282, (4.08, 4.07, 4.10)	1680	8.48(s, 3H, 6a-CH_3), 7.35(s, 3H, 2-CH_3), 5.90(s, 2H, 5-CH_2) 3.45(1H, 10a-H), 2.5(m, 5H, C_6H_5), 1.86(1H, Pm-C_6-H)
IId	255, 284 (4.25, 4.20)	1678	8.46(s, 3H, 6a-CH_3), 7.33(s, 3H, 2-CH_3), 5.88(s, 2H, 5-CH_2) 3.45(1H, 10a-H), 2.75(m, 4H, C_6H_4), 1.85(1H, Pm-C_6-H)
IIe	256, 284 (4.27, 4.23)	1674	8.46(s, 3H, 6a-CH_3), 7.33(s, 3H, 2-CH_3), 5.86(s, 2H, 5-CH_2) 3.45(1H, 10a-H), 2.73(m, 4H, C_6H_4), 1.81(1H, Pm-C_6-H)
IIf	235, 255, 287	1676	8.46(s, 3H, 6a-CH_3), 7.68(s, 3H, C_6H_4-CH_3), 7.33(s, 3H, 2-CH_3) 5.88(s, 2H, 5-CH_2), 3.45(1H, 10a-H), 2.75(m, 4H, C_6H_4), 1.83(1H, Pm-C_6-H)

2-[N-Formyl-N-(2-methyl-4-aminopyrimidin-5-yl)methyl]amino-2-methyltetrahydrofuran-3-yl Methylcarbamthiolate (VI)——A solution of 321 mg of Va in 5 ml of 10% EtOH–H_2O was stirred for 30 min at 50°, then the reaction mixture was evaporated *in vacuo*. The crystalline residue was washed with ether, collected and recrystallized from acetone to give 60 mg (18.5%) of VI, mp 178°. *Anal.* Calcd. for $C_{14}H_{21}O_3N_5S\cdot H_2O$: C, 49.26; H, 6.79; O, 14.07; N, 20.25; S, 19.37. Found: C, 49.65; H, 6.56; O, 14.16; N, 20.56; S, 19.47. UV λ_{max}^{EtOH} mμ (log ε): 235 (3.92), 277 (3.68). IR ν_{max}^{Nujol} cm^{-1}: 3240 (–NH), 1670 (C=O), 1638 (C=O). NMR ($CDCl_3$) τ: 1.70 (s, 1H, NCHO), 1.96 (s, 1H, Pm–C_6–H), 3.91 (b, 2H, Pm–C_4–NH_2), 7.13, 7.20 (d, 3H, NH–$C\underline{H}_2$), 7.53 (s, 3H, Pm–C_2–CH_3), 8.31 (s, 3H, furan–C_2–CH_3).

General Method for the Reaction of IIc with N,N-Disubstituted Carbamoyl Chloride——To a solution of IIc (0.001 mole) in dry pyridine (10 mole), RR'NCOCl (0.0012 mole) was added under ice-cooling. After being stirred at room temperature for 12 hr, the mixture was allowed to stand overnight then the reaction solution was evaporated *in vacuo*. The residue was extracted with $CHCl_3$ and the $CHCl_3$ solution was washed with H_2O successively then dried over anhyd. Na_2SO_4. After removal of the solvent under reduced pressure, the residue was extracted with acetone. The acetone solution was concentrated and the precipitated crystals were refined by recrystallization from acetone.

Reaction of IIc with Dimethylcarbamoyl Chloride——Treatment of 383 mg of IIc with 129 mg of $(CH_3)_2$-NCOCl afforded 2-[N-formyl-N-(2-methyl-4-aminopyrimidin-5-yl)methyl]amino-2-methyltetrahydrofuran-3-yl dimethylcarbamthiolate (VIIa), 104 mg (32.5%), mp 158—160°. *Anal.* Calcd. for $C_{22}H_{28}O_4N_6S\cdot 1/2H_2O$: C, 54.86; H, 6.07; O, 14.95; N, 17.45; S, 6.65. Found: C, 55.28; H, 5.88; O, 14.53; N, 17.54; S, 6.81. UV λ_{max}^{EtOH} mμ (log ε): 252 (4.20), 281 (4.17). IR ν_{max}^{Nujol} cm^{-1}: 1713 (C=O), 1700 (C=O), 1653 (C=O). NMR ($CDCl_3$) τ: −2.05 (b, 1H, NHC_6H_5), 0.48 (b, 1H, NHCO), 1.46 (s, 1H, NCHO), 1.55 (s, 1H, Pm–C_6–H), 7.03 (s, 6H, $N\langle^{CH_3}_{CH_3}$), 7.31 (s, 3H, Pm–C_2–CH_3), 8.26 (s, 3H, furan–C_2–CH_3).

Reaction of IIc with Methylbenzylcarbamoyl Chloride——Treatmwnt of 383 mg of IIc with 215 mg of $C_6H_5CH_2\rangle$NCOCl afforded 2-[N-formyl-N(2-methyl-4-aninopyrimidin-5-yl)methyl]amino-2-methyltetra-

hydrofuran-3-yl methylbenzylcarbamthiolate (VIIb), 312 mg (64%), mp 172—174°. *Anal.* Calcd. for $C_{28}H_{32}O_4N_6S$: C, 61.30; H, 5.88; O, 11.67; N, 15.32; S, 5.83. Found: C, 61.22; H, 5.89; O, 11.85; N, 15.13; S, 16.15. UV λ_{max}^{EtOH} mμ (log ε): 277 (3.79). IR ν_{max}^{Nujol} cm^{-1}: 3220 (-NH), 1704 (C=O), 1670 (C=O), 1640 (C=O). NMR ($CDCl_3$) τ: −0.26 (b, 1H, NHC_6H_5), 0.56 (b, 1H, NHCO), 1.63 (s, 1H, Pm-C_6H), 1.88 (s, 1H, N-CHO), 7.15 (s, 3H, N-CH_3), 7.38 (s, 3H, Pm-C_2-CH_3), 6.23 (s, 3H, furan-C_2-CH_3).

Reaction of IIc with Methyl(triphenylmethyl)carbamoyl Chloride——383 mg of IIc was treated with 361 mg of methyltriphenylmethylcarbamoyl chloride to afford 2-[N-formyl-N-(2-methyl-4-aminopyridine-5-yl)methyl]amino-2-methyltetrahydrofuran-3-yl methyl(triphenylmethyl)carbamthiolate (VIIc), 137 mg (19.1%) as amorphous. *Anal.* Calcd. for $C_{40}H_{40}O_4N_6S \cdot H_2O$: C, 66.84; H, 5.89; O, 11.94; N, 11.69; S, 4.44. Found: C, 66.71; H, 5.78; O, 11.94; N, 11.24; S, 4.64. UV λ_{max}^{EtOH} mμ: 248, 281. IR ν_{max}^{Nujol} cm^{-1}: 3230 (NH), 1705 (C=O), 1650 (C=O). NMR ($CDCl_3$) τ: −2.01 (b, 1H, NHC_6H_5), 0.50 (b, 1H, NHCO), 1.56 (s, 1H, NCHO), 1.70 (s, 1H, Pm-C_6-H), 7.00 (s, 3H, N-CH_3), 7.35 (s, 3H, Pm-C_2-CH_3), 8.46 (s, 3H, furan-C_2-CH_3).

N-(2-Methyl-4-N-phenylcarbamoylaminopyrimidin-5-yl)methyl-N-[2-methyl-3-(methylcarbamoylthio)-tetrahydrofuran-2-yl]formamide (VIII)——a) A solution of VIIc (130 mg) in 6 ml of 5% HCl-EtOH was stirred for 6 hr at 40°. After evaporation of EtOH *in vacuo* at 50°, the residue was dissolved in H_2O. The aqueous solution was neutralized with $NaHCO_3$ 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 solvent, the residue was chromatographed on the silica gel column. Eluation with AcOEt afforded VIII (poor yield), mp 187—189° (decomp.). *Anal.* Calcd. for $C_{21}H_{26}O_4N_6S$: C, 55.01; H, 5.72; O, 13.96; N, 18.33; S, 6.98. Found: C, 54.77; H, 8.72; O, 13.85; N, 18.34; S, 7.07. UV λ_{max}^{EtOH} mμ (log ε): 252 (3.19), 281 (3.68). IR ν_{max}^{Nujol} cm^{-1}: 3240 (NH), 1703 (C=O), 1673 (C=O). NMR ($CDCl_3$) τ: −1.93 (b, 1H, NH-C_6H_5), 0.63 (b, 1H, NHCO), 1.56 (s, 1H, N-CHO), 1.66 (s, 1H, Pm-C_6-H), 7.12, 7.13 (d, 3H, NH-CH_3), 7.35 (s, 3H, Pm-C_2-CH_3), 8.25 (s, 3H, furan-C_2-CH_3).

b) To a solution of VI (90 mg) in dry DMF (5 ml) phenylisocyanate (60 mg) was added at room temperature. After being stirred for 2 hr, the reaction mixture was allowed to stand overnight. The reaction mixture was concentrated *in vacuo* at 70° and the residue was extracted with $CHCl_3$. The $CHCl_3$ solution was treated as described in a), to afford VIII (mp 187—189°, 26 mg, 21.5%) which was identified with VIII obtained by method a) by the comparison of IR spectrum.

General Procedure for Reaction of I with Isocyanate Derivatives in Chloroform——To a solution of I (0.005 mole) in $CHCl_3$ (20 ml) RNCO (0.005 mole) was added at room temperature and the mixture was allowed to stand overnight then stirred for 6 hr, washed with H_2O, and dried over anhyd. Na_2SO_4. After removal of the solvent under reduced pressure, the crystalline residue was eluted with acetone on silica gel and the isolated compounds were refined by recrystallization from acetone.

Reaction of I with Ethylisocyanate in Chloroform——A solution of I (1.32 g) in chloroform (20 ml) was treated with EtNCO (0.355 g) to afford IIb (0.51 g, 34.2%, mp 122—123°).

Reaction of I with Phenylisocyanate in Chloroform——I (1.32 g) was treated with PhNCO (0.54 g) to afford IIc (0.52 g, 39.4%, mp 175°).