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Studies on Heterocyclic Enaminonitriles. III.[1] Reactions of 2-Benzamido-3-cyano-4,5-dihydrothiophenes with Amines

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The reaction of 2-benzamido-3-cyano-4,5-dihydrothiophene (I) with cyclohexylamine gave 4-cyclohexylamino-2-phenyl-5,6-dihydrothieno[2,3-*d*]pyrimidine (IVa) in 93% yield. Similarly, I reacted with morpholine, piperidine and pyrrolidine to yield the corresponding 4-amino-2-phenyl-5,6-dihydrothieno[2,3-*d*]pyrimidines (IVb—d). In a similar manner, 2-benzamido-3-cyano-5-methyl(or 4-phenyl)-4,5-dihydrothiophene (II or III) reacted with amines to form the 4-amino derivatives (Va—d or VIa—d) corresponding to IVa—d. On the other hand, I, II and III were converted on treatment with dimethylamine hydrochloride in pyridine to the corresponding 2-phenyl-5,6-dihydrothieno[2,3-*d*]pyrimidin-4(3*H*)-ones (VII—IX). Compounds IVa—d, Va—d and VIa—d were also synthesized from 4-chloro-2-phenyl-5,6-dihydrothieno[2,3-*d*]pyrimidines and appropriate amines.

Keywords——amine; 2-benzamido-3-cyano-4,5-dihydrothiophene; 4-substituted-2-phenyl-5,6-dihydrothieno[2,3-*d*]pyrimidine; cyclization; 2-phenyl-5,6-dihydrothieno[2,3-*d*]-pyrimidin-4(3*H*)-one

Breukink *et al.*[2] reported that 2-acetamidobenzonitrile (**1**) reacts with sodium methoxide to form 4-methoxy-2-methylquinazoline (**3**). This reaction occurs *via* addition to give the imino ether (**2**), which undergoes intramolecular dehydration to yield **3**.

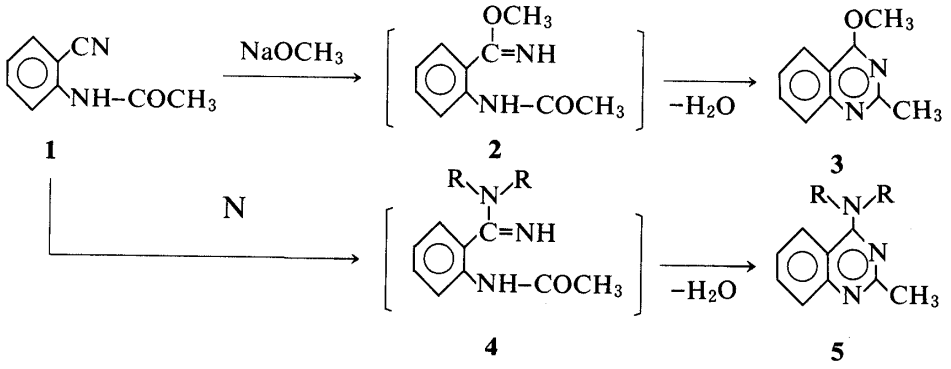


Chart 1

This reaction suggests the possibility that when an amine is used in place of sodium methoxide, an amidine (**4**) initially formed may undergo intramolecular dehydration to produce a 4-aminoquinazoline derivative (**5**). In the preceding paper,[1] we reported a synthesis of 2-amino-3-cyano-4,5-dihydrothiophenes. The present paper deals with the reactions of 2-benzamido-3-cyano-4,5-dihydrothiophene (I) and 2-benzamido-3-cyano-5-methyl(or 4-phenyl)-4,5-dihydrothiophene (II or III) with amines.

When a mixture of I and cyclohexylamine (4 eq) was heated at 120°C for 5 h, 4-cyclohexylamino-2-phenyl-5,6-dihydrothieno[2,3-*d*]pyrimidine (IVa) was obtained in 93% yield. The results of elemental analysis and the mass spectrum (MS) (M^+ m/z: 311) of IVa indicated that this compound had the molecular composition $C_{18}H_{21}N_3S$. Its infrared (IR)

spectrum exhibited a secondary amino band at 3430 cm^{-1}, but lacked a characteristic nitrile band. The proton magnetic resonance (PMR) spectrum showed a broad multiplet at δ 3.95—4.35 (2H) due to an amino proton and the C_1-proton of the cyclohexane ring, and a multiplet at δ 0.9—2.3 (10H) assignable to the other protons of the cyclohexane ring, in addition to signals due to five protons of the 2-phenyl group and four protons of the dihydrothiophene moiety. These data are consistent with the proposed structure. Furthermore, the structure of IVa was confirmed by direct comparison with an authentic sample prepared from 4-chloro-2-phenyl-5,6-dihydrothieno[2,3-*d*]pyrimidine and cyclohexylamine by the method described later in this paper.

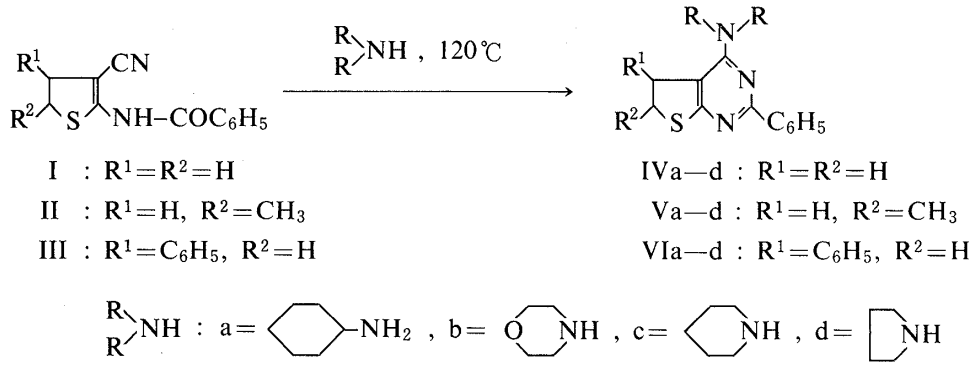
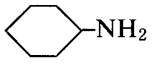
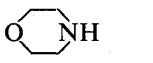
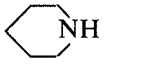
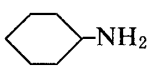
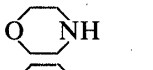
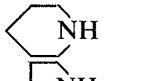
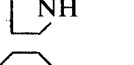
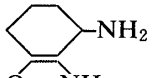
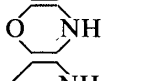
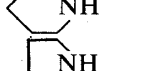
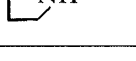


Chart 2

TABLE I. Some Properties of IVa—d, Va—d and VIa—d

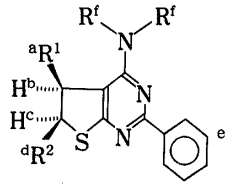
Compd. No.	R NH R	Yield (%) ( )[a]		mp (°C) (Recrystn. solvent)	Appearance (Colorless)	Formula	Analysis (%) Calcd (Found) C	H	N
IVa		93	(83)	172—173 (Acetone-Petr. ether)	Prisms	$C_{18}H_{21}N_3S$	69.43 (69.63	6.80 6.78	13.50 13.27)
IVb		72	(80)	174—175 (Acetone)	Needles	$C_{16}H_{17}N_3OS$	64.20 (64.23	5.72 5.72	14.04 14.05)
IVc		84	(87)	148—150 (Acetone)	Needles	$C_{17}H_{19}N_3S$	68.66 (68.84	6.44 6.41	14.13 14.47)
IVd		87	(83)	193—194 (Acetone)	Needles	$C_{16}H_{17}N_3S$	67.82 (67.85	6.05 6.05	14.83 14.54)
Va		96	(83)	153—155 (CH_2Cl_2-Petr. benzin)	Columns	$C_{19}H_{23}N_3S$	70.13 (70.06	7.12 7.16	12.91 12.72)
Vb		74	(77)	155 (Acetone)	Needles	$C_{17}H_{19}N_3OS$	65.16 (65.32	6.11 6.03	13.41 13.11)
Vc		79	(84)	147 (CH_2Cl_2-Ether)	Needles	$C_{18}H_{21}N_3S$	69.43 (69.42	6.80 6.77	13.50 13.21)
Vd		81	(92)	162—163 (CH_2Cl_2-Ether)	Columns	$C_{17}H_{19}N_3S$	68.66 (68.74	6.44 6.40	14.13 14.18)
VIa		79	(84)	139—141 (Ether-Petr. benzin)	Prisms	$C_{24}H_{25}N_3S$	74.39 (74.58	6.50 6.48	10.85 10.62)
VIb		81	(93)	202—203 (Acetone)	Prisms	$C_{22}H_{21}N_3OS$	70.38 (70.68	5.64 5.69	11.19 10.84)
VIc		77	(95)	199—201 (Acetone)	Prisms	$C_{23}H_{23}N_3S$	73.97 (73.74	6.21 6.03	11.25 10.92)
VId		82	(95)	219—221 (Acetone)	Prisms	$C_{22}H_{21}N_3S$	73.51 (73.63	5.89 5.83	11.69 11.69)

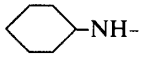
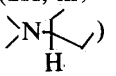
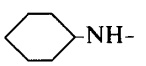
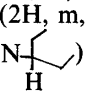
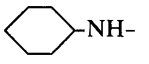
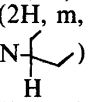
a) Yields from the reactions of X, XI and XII with amines.

Morpholine, piperidine and pyrrolidine reacted with I under the same conditions to give the corresponding 4-substituted-2-phenyl-5,6-dihydrothieno[2,3-*d*]pyrimidines (IVb—d).

Similarly, the reactions of II and III with cyclohexylamine, morpholine, piperidine and pyrrolidine resulted in the formation of the 4-amino-2-phenyl-5,6-dihydrothieno[2,3-*d*]-

TABLE II. Some Spectral Data for IVa—d, Va—d and VIa—d



Compd. No.	R_2N-	^{1}H-NMR spectra (ppm) in $CDCl_3$ solution (J in Hz)						MS m/z (M^+)
		H^a	H^b	H^c	H^d	H^e	H^f	
IVa		2.85—3.20 (m)		3.25—3.58 (m)		7.26—7.56 (3H, m) 8.35—8.56 (2H, m)	0.9—2.3 (10H, m) 3.95—4.35(2H, m, >NH and >N- 	311
IVb		3.28 (s)				7.28—7.50 (3H, m) 8.22—8.44 (2H, m)	3.52—3.84 (8H, m)	299
IVc		3.27 (s)				7.28—7.48 (3H, m) 8.28—8.44 (2H, m)	1.58—1.74 (6H, m) 3.46—3.75 (4H, m)	297
IVd		3.30 (d)			3.48 (d) (J=7)	7.34—7.48 (3H, m) 8.32—8.46 (3H, m)	1.84—2.04 (4H, m) 3.64—3.85 (4H, m)	283
Va		3.11 (dd)	2.59 (dd)	3.68— 4.16 (m)	1.46 (d)	7.16—7.36 (3H, m) 8.07—8.18 (2H, m)	0.8—2.2 (10H, m) 3.68—4.16 (2H, m, >NH and >N- 	325
		($J_{a,b}$=14, $J_{a,c}$=8, $J_{b,c}$=6, $J_{c,d}$=7)						
Vb		3.51 (dd)	2.95 (dd)	3.58— 4.20 (m)	1.52 (d)	7.38—7.64 (3H, m) 8.25—8.60 (2H, m)	3.58—3.93 (8H, m)	313
		($J_{a,b}$=15, $J_{a,c}$=8, $J_{b,c}$=6, $J_{c,d}$=7)						
Vc		3.50 (dd)	2.95 (dd)	3.76— 4.13 (m)	1.50 (d)	7.38—7.61 (3H, m) 8.25—8.61 (2H, m)	1.48—1.91 (6H, m) 3.50—3.73 (4H, m)	311
		($J_{a,b}$=15, $J_{a,c}$=8, $J_{b,c}$=6, $J_{c,d}$=7)						
Vd		3.53 (dd)	3.07 (dd)	3.64— 3.88 (m)	1.42 (d)	7.16—7.32 (3H, m) 8.12—8.28 (2H, m)	1.78—1.96 (4H, m) 3.54—3.72 (4H, m)	297
		($J_{a,b}$=14, $J_{a,c}$=8, $J_{b,c}$=6, $J_{c,d}$=7)						
VIa		7.29 (s)	4.51 (dd)	3.25 (dd)	3.69 (dd)	7.22—7.44 (3H, m) 8.26—8.40 (2H, m)	0.6—2.0 (10H, m) 3.67—4.20 (2H, m, >NH and >N- 	387
		($J_{b,c}$=8, $J_{b,d}$=9, $J_{c,d}$=11)						
VIb		7.00— 7.60 (m)	4.78 (dd)	3.11 (dd)	3.73 (dd)	7.00—7.60 (3H, m) 8.24—8.48 (2H, m)	3.20—3.68 (8H, m)	375
		($J_{b,c}$=5, $J_{b,d}$=9, $J_{c,d}$=11)						
VIc		6.88— 7.32 (m)	4.72 (dd)	2.99 (dd)	3.66 (dd)	6.88—7.32 (3H, m) 8.15—8.30 (2H, m)	0.88—1.56 (6H, m) 3.24—3.44 (4H, m)	373
		($J_{b,c}$=5, $J_{b,d}$=9, $J_{c,d}$=11)						
VId		6.84— 7.32 (m)	4.92 (dd)	2.98 (dd)	3.79 (dd)	6.84—7.32 (3H, m) 8.20—8.32 (2H, m)	1.64—1.80 (4H, m) 3.20—3.64 (4H, m)	359
		($J_{b,c}$=2, $J_{b,d}$=8, $J_{c,d}$=11)						

Abbreviations: d, doublet; dd, doublet of doublets; m, multiplet; s, singlet.

pyrimidines (Va—d and VIa—d) corresponding to IVa—d. The structures of IVa—d, Va—d and VIa—d were confirmed by direct comparison with authentic specimens prepared by an alternative route. These structures were also supported by the analytical (Table I) and spectral data (Table II).

On the other hand, when a solution of I and dimethylamine hydrochloride (2 eq) in pyridine was refluxed for 5 h, 2-phenyl-5,6-dihydrothieno[2,3-*d*]pyrimidin-4(3*H*)-one (VII) was obtained in 92% yield, and no formation of the expected 4-dimethylamino-2-phenyl-5,6-dihydrothieno[2,3-*d*]pyrimidine was noted (Chart 3).

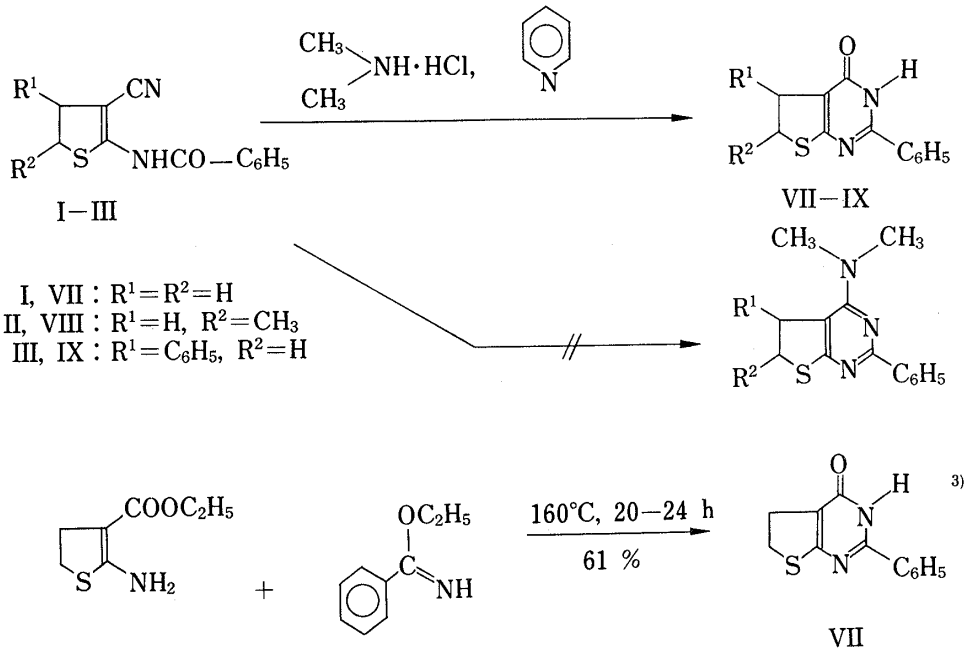
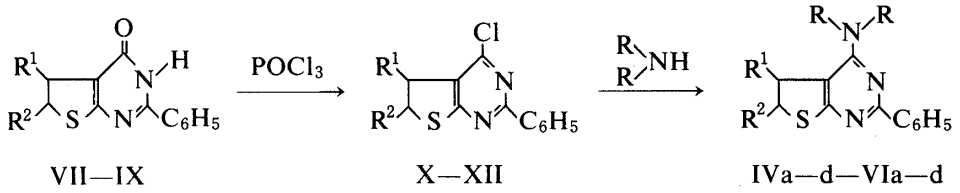


Chart 3

The structure of VII was confirmed by direct comparison with an authentic specimen.[3] In a similar manner, compounds II and III provided 6-methyl-2-phenyl-5,6-dihydrothieno[2,3-*d*]pyrimidin-4(3*H*)-one (VIII) and 2,5-diphenyl-5,6-dihydrothieno[2,3-*d*]-pyrimidin-4(3*H*)-one (IX) in 93 and 90% yields, respectively. Generally, *o*-acylaminonitriles undergo acid-catalyzed intramolecular cyclization on treatment with an acid, to give condensed 4(3*H*)-pyrimidinones.[4] For example, 2-acetamidonaphthalene-1-carbonitrile is cyclized to 3-methylbenzo[*f*]quinazolin-1(2*H*)-one by treatment with dry hydrogen chloride in absolute ethanol.[5] Similarly, we showed[6] that 2-benzamido-3-cyano-1-ethoxycarbonyl-4-phenyl-4,5-dihydropyrrole is converted to 7-ethoxycarbonyl-2,5-diphenyl-5,6-dihydropyrrolo[2,3-*d*]-pyrimidin-4(3*H*)-one. Therefore, dimethylamine hydrochloride seems to behave only as an acid in the above reaction.

In order to confirm the structures of IVa—d, Va—d and VIa—d, we synthesized them by an alternative route. On chlorination with phosphoryl chloride, VII and VIII were converted to the corresponding 4-chloro derivatives (X and XI). Compound IX was chlorinated to provide 4-chloro-2,5-diphenyl-5,6-dihydrothieno[2,3-*d*]pyrimidine (XII) by heating it with phosphorus pentachloride in phosphoryl chloride. When a solution of X and cyclohexylamine (5 eq) in acetonitrile was refluxed for 10 h, the desired IVa was obtained in 83% yield. Compound X reacted with morpholine, piperidine and pyrrolidine in a similar fashion to produce IVb, IVc and IVd in yields of 80, 87 and 83%, respectively. Similarly, the reactions of XI and XII with cyclohexylamine, morpholine, piperidine and pyrrolidine gave Va—d and VIa—d, respectively.



VII—IX X—XII IVa—d—VIa—d

VII, X, IV : $R^1=R^2=H$
VIII, XI, V : $R^1=H$, $R^2=CH_3$
IX, XII, VI : $R^1=C_6H_5$, $R^2=H$

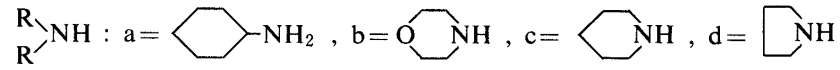


Chart 4

Further studies on the reactions of 2-benzamido-3-cyano-4,5-dihydrothiophenes with nucleophiles other than amines are in progress.

Experimental

All melting points are uncorrected. IR spectra were recorded on a JASCO IRA-2 spectrophotometer. PMR spectra were taken on a Hitachi R-22 spectrometer at 90 MHz or a JNM-MH-100 spectrometer at 100 MHz using tetramethylsilane as an internal standard. Mass spectra were measured with a JEOL model JMS-01SG spectrometer.

Reactions of 2-Benzamido-3-cyano-4,5-dihydrothiophenes (I, II and III) with Amines. General Procedure——A mixture of I, II or III (5 mmol) and an amine (20 mmol) was heated at 120 °C for 5 h on an oil-bath. The reactants were acidified with 5% HCl, and extracted with $CHCl_3$. The $CHCl_3$ layer was washed with water, and dried over $MgSO_4$. After removal of the $CHCl_3$ by evaporation, the residue was recrystallized from the solvent listed in Table I to give the corresponding 4-amino-2-phenyl-5,6-dihydrothieno[2,3-*d*]pyrimidine (IVa—d, Va—d or VIa—d).

Preparation of 2-Phenyl-5,6-dihydrothieno[2,3-*d*]pyrimidin-4(3*H*)-ones (VII, VIII and IX)——A solution of I, II or III (10 mmol) and dimethylamine hydrochloride (20 mmol) in pyridine (10 ml) was refluxed for 5 h. After removal of the pyridine *in vacuo*, the residue was poured into ice water. The precipitate was collected, washed with water, and dried. Compound VII, VIII or IX was obtained in 92, 93 or 90% yield, respectively.

i) 2-Phenyl-5,6-dihydrothieno[2,3-*d*]pyrimidin-4(3*H*)-one (VII) was recrystallized from CH_3OH–CH_2Cl_2 to give colorless needles, mp 262—264 °C (lit.,[3] 251—255 °C); this product was identical with an authentic sample.[3]

ii) 6-Methyl-2-phenyl-5,6-dihydrothieno[2,3-*d*]pyrimidin-4(3*H*)-one (VIII) was recrystallized from CH_3OH–$CHCl_3$ to produce colorless prisms, mp 230—232 °C. *Anal.* Calcd for $C_{13}H_{12}N_2OS$: C, 63.92; H, 4.95; N, 11.47. Found: C, 63.86; H, 4.86; N, 11.52. MS *m/z*: 244 (M^+). IR ν_{max}^{KBr} cm^{-1}: 1630 (>CO). PMR (in DMSO-d_6) δ: 1.43 (3H, d, J=7 Hz, C_6-C<u>H</u>$_3$), 2.79 (1H, dd, J=16, 6 Hz, C_5-H), 3.32 (1H, dd, J=16, 8 Hz, C_5-H), 3.87—4.20 (1H, m, C_6-H), 7.41—7.62 (3H, m, aromatic H), 8.00—8.14 (2H, m, aromatic H), 12.3—12.7 (1H, br s, >NH).

iii) 2,5-Diphenyl-5,6-dihydrothieno[2,3-*d*]pyrimidin-4(3*H*)-one (IX) was recrystallized from CH_3OH–$CHCl_3$ to yield colorless needles, mp 286—288 °C. *Anal.* Calcd for $C_{18}H_{14}N_2OS$: C, 70.58; H, 4.61; N, 9.15. Found: C, 70.41; H, 4.57; N, 9.11. MS *m/z*: 306 (M^+). IR ν_{max}^{KBr} cm^{-1}: 1637 (>CO). PMR (in DMSO-d_6) δ: 3.24 (1H, dd, J=12, 4 Hz, C_6-H), 4.03 (1H, dd, J=12, 10 Hz, C_6-H), 4.73 (1H, dd, J=10, 4 Hz, C_5-H), 7.40 (5H, s, aromatic H), 7.58—7.72 (3H, m, aromatic H), 8.14—8.28 (2H, m, aromatic H), 12.6—12.9 (1H, br s, >NH).

Reactions of VII and VIII with Phosphoryl Chloride——A solution of VII or VIII (5 mmol) in $POCl_3$ (10 ml) was refluxed for 2 h. After removal of the $POCl_3$ under reduced pressure, the residue was poured into ice water. The precipitate was collected, washed with water, and air-dried.

i) 4-Chloro-2-phenyl-5,6-dihydrothieno[2,3-*d*]pyrimidine (X) was recrystallized from acetone to give colorless prisms (1.19 g, 96%), mp 139—141 °C. *Anal.* Calcd for $C_{12}H_9ClN_2S$: C, 57.96; H, 3.65; N, 11.27. Found: C, 57.92; H, 3.83; N, 11.39. MS *m/z*: 248 (M^+). PMR (in $CDCl_3$) δ: 3.45 (4H, s, C_5-H and C_6-H), 7.48—7.64 (3H, m, aromatic H), 8.43—8.56 (2H, m, aromatic H).

ii) 4-Chloro-6-methyl-2-phenyl-5,6-dihydrothieno[2,3-*d*]pyrimidine (XI) was recrystallized from acetone–

petr. ether to yield colorless prisms (1.16 g, 89%), mp 116°C. *Anal.* Calcd for $C_{13}H_{11}ClN_2S$: C, 59.43; H, 4.22; N, 10.67. Found: C, 59.46; H, 4.32; N, 10.67. MS *m/z*: 262 (M^+). PMR (in $CDCl_3$) δ: 1.48 (3H, d, J=7 Hz, C_6-CH_3), 2.87 (1H, dd, J=16, 7 Hz, C_5-H), 3.39 (1H, dd, J=16, 8 Hz, C_5-H), 3.75—4.06 (1H, m, C_6-H), 7.12—7.32 (3H, m, aromatic H), 8.04—8.18 (2H, m, aromatic H).

Preparation of 4-Chloro-2,5-diphenyl-5,6-dihydrothieno[2,3-*d*]pyrimidine (XII)——A mixture of IX (5 mmol) and PCl_5 (5 mmol) in $POCl_3$ (10 ml) was refluxed for 5 h. After removal of the $POCl_3$ *in vacuo,* the residue was poured into ice water, and the solution was basified with NH_4OH, and extracted with $CHCl_3$. The $CHCl_3$ extract was dried over Na_2SO_4, and concentrated. The residue was recrystallized from ether–petr. ether to give XII (930 mg, 57%) as colorless prisms, mp 107—109°C. *Anal.* Calcd for $C_{18}H_{13}ClN_2S$: C, 66.57; H, 4.04; N, 8.63. Found: C, 66.42; H, 4.07; N, 8.63. MS *m/z*: 324 (M^+). PMR (in $CDCl_3$) δ: 3.34 (1H, dd, J=12, 4 Hz, C_6-H), 4.01 (1H, dd, 10 Hz, C_6-H), 4.84 (1H, dd, J=10, 4 Hz, C_5-H), 7.36 (5H, s, aromatic H), 7.48—7.60 (3H, m, aromatic H), 8.44—8.60 (2H, m, aromatic H).

Reactions of 4-Chloro-2-phenyl-5,6-dihydrothieno[2,3-*d*]pyrimidines (X, XI and XII) with Amines. General Procedure——A solution of X, XI or XII (2 mmol) and an amine (10 mmol) in CH_3CN (10 ml) was refluxed for 10 h. After removal of the solvent *in vacuo,* the residue was acidified with 5% HCl, and extracted with $CHCl_3$. The $CHCl_3$ layer was washed with water, and then concentrated *in vacuo.* The residue was recrystallized from an appropriate solvent (Table I) to give IVa—d, Va—d or VIa—d in the yields shown in Table I.

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