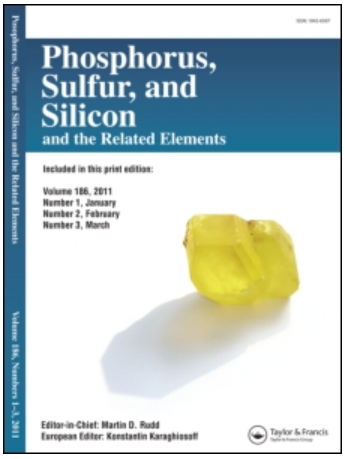

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SYNTHESIS AND REACTIONS OF SOME NEW THIENO[2,3-*b*]-PYRIDINES AND THE ANTIMICROBIAL EFFECTS

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SYNTHESIS AND REACTIONS OF SOME NEW THIENO[2,3-*b*]-PYRIDINES AND THE ANTIMICROBIAL EFFECTS

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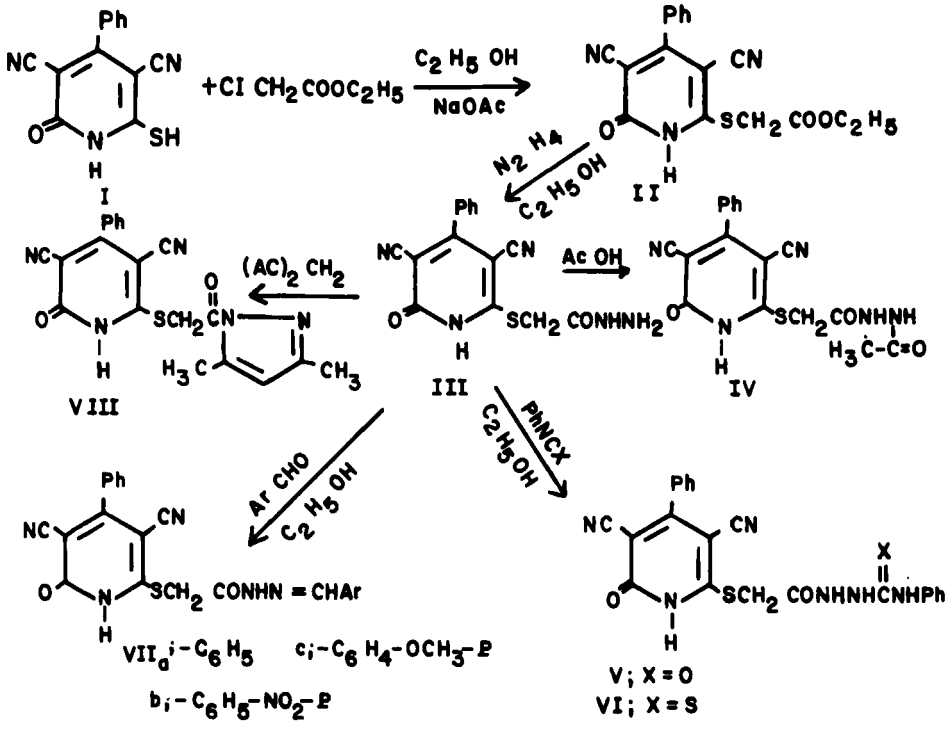
3,5-Dicyano-6-mercapto-4-phenylpyridin-2(1**H**)-one (**I**) was reacted with ethyl chloroacetate to give compound (**II**) which on reaction with hydrazine hydrate gave the corresponding hydrazide derivative (**III**). Acylation of (**III**) with acetic acid, phenylisocyanate, or phenylisothiocyanate gave different monoacyl derivatives (**IV–VI**). Condensation of **III** with aromatic aldehydes and acetylacetone gave compounds **VII**$_{a-c}$, **VIII** respectively. Compound I was reacted with chloroanilides, bromoacetone and phenacyl bromide to yield the **IX–XI**; these and compound **II** gave thieno[2,3-*b*]-pyridines (**XII–XV**) on treatment with sodium ethoxide solution. Reaction of **XII** with acetic anhydride gave the diacetyl derivative **XVI**. Hydrolysis of compound **XII** with sodium hydroxide gave the corresponding acid (**XVII**) which on treatment with acetic anhydride gave the oxazine derivative (**XVIII**). Reaction of oxazine compound **XVIII** with ammonium acetate and hydrazine hydrate gave pyrido[3′,2′:4,5] thieno[3,2-*d*]pyrimidin-4,7-dione derivative (**XIX**) and (**XX**) respectively. The *N*-amino derivative (**XX**) was reacted with 4-nitrobenzaldehyde to give the corresponding azomethine (**XXI**).

Significant in vitro gram-positive and gram negative antibacterial activities as well as anti-fungal effect were observed for some members of the series.

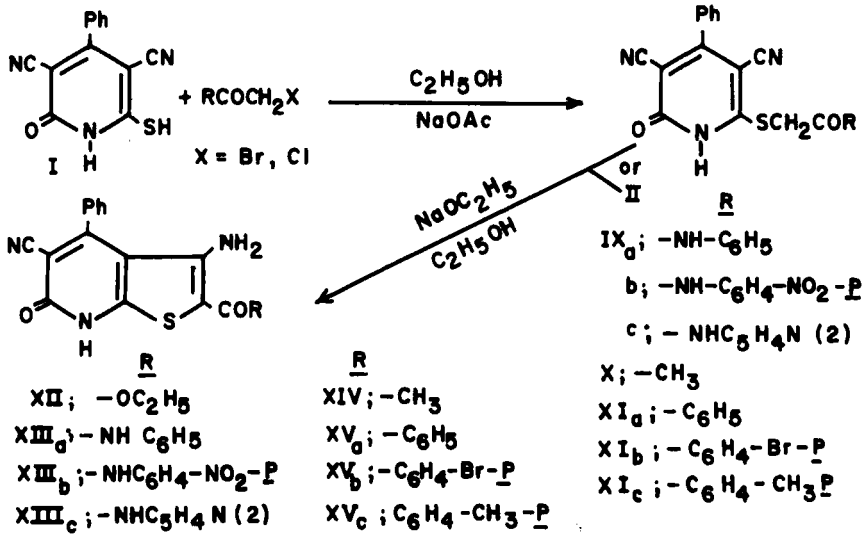
Key words: Thieno[2,3-*b*]-pyridines; synthesis; reactions and antimicrobial effects.

Many thienopyridines have been investigated because of the variable biological activities such as against diabetes mellitus, as analgesics, as anti-inflammatories, as sedatives and as anticoagulants.[1–9] The versatile biological properties of thienopyridines prompted us to study the synthesis of new thienopyridines using 3,5-dicyano-6-mercapto-4-phenylpyridin-2(1**H**)-one (**I**)[10] as starting material. This was reacted with ethylchloroformate in ethanol in presence of KOH to give **II**. Treatment of **II** with hydrazine hydrate in ethanol gave the corresponding hydrazide derivative (**III**) (c.f. Scheme 1 and Table I). The hydrazide derivative (**III**) were easily acylated using acetic acid to give the *N*-acetyl derivative (**IV**), with phenylisocyanate and phenylisothiocyanate to give the semicarbazide and thiosemicarbazide derivatives (**V, VI**) respectively (c.f. Scheme 1 and Table I). The hydrazide derivative (**III**) was found to undergo several condensation reactions smoothly with aromatic aldehydes in ethanol to give the corresponding hydrazones (**VII**$_{a-c}$) (c.f. Scheme 1 and Table I). On the other hand acetylacetone reacted with **III** to give the pyrazolo derivative (**VII**).

Compound **I** was reacted with chloroanilides, bromoacetone phenacyl bromides in ethanol containing anhydrous sodium acetate to give the derivatives (**IX–XI**) (c.f. Scheme 2 and Table II). Thieno[2,3-*b*] pyridine derivatives (**XII–XV**) (c.f. Scheme 2 and Table II) were obtained upon treatment of compounds (**II, IX–XI**) with ethanolic sodium ethoxide solution using the method of Guerrera.[11] Compounds (**XII–XV**) are characterized with the disappearance of signals at δ 3.8, characteristic in the ^{1}H NMR for an S—CH_2 group, and for a NH_2 group in the



SCHEME 1



SCHEME 2

TABLE I

Physical and analytical data of compounds II–VIII

nd	M.P. [°C] (solvent)	Yield % colour	Molecular formula	Elemental analysis calculated/found C	H	N	S	I.R. cm^{-1}	^1H NMR δ
	198 (Ethanol)	80 Yellow	$C_{17}H_{13}N_5O_3S$	60.17 60.38	3.83 4.11	12.38 12.20	9.43 9.61	3500, 3380(NH)2220 (CN), 1730, 1670(C=O)	1.1–1.4(t, 3H, CH_3) 3.8(s, 2H, CH_2) 4.0–4.3(q, 2H, CH_2) 5.6(s, 1H, NH), 7.4 (s, 5H, Ar.)
	254 (Ethanol)	78 White	$C_{15}H_{11}N_5O_2S$	55.38 55.20	3.38 3.23	21.53 21.81	9.84 9.96	3400(NH), 3340— 3220(NH, NH_2) 2230, 2220(CN) 1660(C=O)	3.8(s, 2H, CH_2) 4.3(s, 2H, NH_2), 7.5 (s, 5H, Ar.), 7.9(s, 1H, N 9.1(s; H, NH)
	285 (Ethanol)	76 White	$C_{17}H_{13}N_5O_3S$	55.58 55.60	3.54 3.90	19.07 18.85	8.71 8.61	3420, 3340, 3240 3180(NH), 2220(CN), 1700, 1670, 1650(C=O)	2.1(s, 3H, CH_3), 4.2(s, 2H, CH_2), 7.8(s, 5H, Ar.), 8.2, 10.2 NH).
	235 (Ethanol)	57 White	$C_{22}H_{16}N_6O_3S$	59.45 58.97	3.60 3.47	18.91 18.70	7.20 7.44	3400-3220(NH) 2220, 2230(CN) 1720, 1665, 1650(C=O).	3.9(s, 2H, CH_2), 7.0–7.7(m, 10H, Ar.), 8, 8.7, 9.8(s, 4H, 4NH).
	240 (Ethanol)	66 Pale yellow	$C_{22}H_{16}N_6O_2S_2$	57.39 57.23	3.47 3.64	18.26 17.93	13.91 13.84	3500-3240(NH) 2240(CN, 1700, 1650 (C=O).	—
	262 (Ethanol)	76 White	$C_{22}H_{15}N_5O_2S$	63.92 63.81	3.63 3.88	16.94 16.96	7.79 7.59	3400, 3360(NH) 2240(CN), 1680 1650(C=O)	4.3(s, 2H, CH_2), 4.8(s, 1 7.5–8.1(m, 10H, Ar.) 8.2(s, 1H, NH), 8.4(s, 1H
	290 (Acetic acid)	81 Yellow	$C_{22}H_{14}N_6O_4S$	57.64 57.43	3.05 3.31	18.34 18.54	6.98 7.13	3370, 3300(NH) 2220(CN), 1670, 1650(C=O)	—
	265 (Acetic acid)	70 Pale yellow	$C_{23}H_{17}N_5O_3S$	62.30 62.54	3.83 3.71	15.80 15.88	7.22 7.34	3360, 3220(NH) 2220(CN), 1680, 1650(C=O)	—
	255 (Ethanol)	60 Pale yellow	$C_{20}H_{15}N_5O_2S$	61.69 61.60	3.85 3.74	17.99 18.31	8.22 8.54	3480, 3360(NH), 2220(CN), 1720, 1660(C=O).	2.3(s, 3H, CH_3), 2.7(s, 3 3.4(s, 2H, CH_2), 6.2(s, 1 7.6(s, 5H, Ar.), 8.1(s, 1H

TABLE II

Physical and analytical data of compounds IX–XX

ound	M.P. [°C] (solvent)	Yield % colour	Molecular formula	Elemental analysis calculated/found					I.R. cm^{-1}	^1H NM
				C	H	N	S	Br		
	260	73	$C_{21}H_{14}N_4O_2S$	65.28	3.62	14.50	8.29	—	3450, 3320(NH)	4.1(s, 2H.
	(Ethanol)	Pale yellow		65.49	3.75	14.69	8.40	—	2240(CN), 1670, 1650(C=O).	6.9–7.71 2NH and
	276	76	$C_{21}H_{13}N_5O_4S$	58.46	2.32	16.24	7.42	—	3420, 3280(NH)	—
	(Acetic acid)	Pale yellow		58.41	2.61	16.45	7.62	—	2220(CN), 1690, 1660(C=O).	
	220	72	$C_{20}H_{13}N_5O_2S$	62.01	3.35	18.08	8.26	—	3400, 3240(NH)	—
	(Ethanol)	White		62.32	3.46	18.29	8.11	—	2220(CN), 1700, 1650(C=O).	
	175	65	$C_{16}H_{11}N_3O_2S$	62.13	3.55	13.59	10.35	—	3460, 3340(NH)	2.3(s, 3H.
	(Ethanol)	White		62.54	3.61	13.80	10.21	—	2220(CN), 1740 1650(C=O)	3.9(s, 2H. 5.6(s, 1H. 7.5(s, 5H.
	255	80	$C_{21}H_{13}N_3O_2S$	69.92	3.50	11.32	8.62	—	3460, 3380(NH)	—
	(Acetic acid)	Pale yellow		68.34	3.39	11.54		—	2220(CN)1670, 1650(C=O)	
	245	76	$C_{21}H_{12}BrN_3O_2S$	56.09	2.66	9.33	7.11	17.77	3480, 3360(NH)	—
	(Acetic acid)	Pale yellow		56.33	2.86	9.49	7.20	17.52	2240(CN), 1680 1650(C=O)	
	260	72	$C_{22}H_{15}N_3O_2S$	68.58	3.89	10.90	8.31	—	3460, 3340(NH)	2.5(s, 3H.
	(Ethanol)	White		68.46	3.68	10.98	8.48	—	2240(CN), 1670 1650(C=O)	4.7(s, 2H. 6.4(s, 1H. 7.2–7.8(m Ar.)
	270	60	$C_{17}H_{13}N_3O_3S$	60.17	3.83	12.38	9.43	—	3500, 3380(NH)	1.1, 1.4(t. CH_2)
	(Ethanol)	Yellow		59.90	4.20	12.50	9.61	—	3300, 3180(NH_2) 2220(CN), 1680 1650(C=O)	3.9–4.2(q CH_2) 5.3(s, 1H 7.2–7.6 7H NH

[a]	274	58 Yellow	$C_{21}H_{14}N_4O_2S$	65.28 65.40	3.62 3.89	14.50 14.66	8.29 8.11	— —	3500, 3400(NH_2) 3320(NH), 2220 (CN), 1650(C=O).	5.7(s, 2H, NH_2), 6 1H, NH 6.8–7.7(m Ar.), 8. 1H, NH
[b]	310 (Acetic acid)	65 Yellow	$C_{21}H_{13}N_5O_4S$	58.46 58.33	2.32 2.46	16.24 16.39	7.42 7.64	— —	3480, 3400(NH_2) 3300(NH), 2240 (CN), 1650(C=O)	—
[c]	285 (Ethanol)	60 Yellow	$C_{20}H_{13}N_5O_2S$	62.01 62.30	3.35 3.48	18.08 18.22	8.26 8.40	— —	3500, 3400(NH_2) 3300(NH), 2220 (CN), 1650(C=O)	—
	278 (Ethanol)	76 Yellow	$C_{16}H_{11}N_3O_2S$	62.30 62.13	3.55 3.68	13.59 13.80	10.55 10.61	— —	3500(NH), 3340 3440(NH_2), 2230 (CN), 1690, 1650(C=O)	2.3(s, 3H, CH_3), 5 1H, NH 6.3(s, 2I NH_2) 7.3–7.6(m Ar.)
	355 (DMF)	76 Orange	$C_{21}H_{13}N_3O_2S$	67.92 68.30	3.50 3.91	11.32 11.60	8.62 8.51	— —	3500, 3400(NH_2) 3280(NH), 2240 (CN), 1640(C=O).	—
	338 (Acetic acid)	70 Orange	$C_{21}H_{12}BrN_3O_2S$	56.09 56.30	2.66 2.51	9.33 9.47	7.11 7.31	17.77 17.91	3480, 3360(NH_2) 3300(NH), 2220 (CN), 1650(C=O)	—
	298 (Chloroform)	68 Yellow	$C_{22}H_{15}N_3O_2S$	68.57 68.90	3.89 3.76	10.90 10.78	8.31 8.23	— —	3500, 3400(NH_2) 3260(NH), 2240 (CN), 1650 (C=O).	2.3(s, 3H. 5.4(s, 1H. 6.6(s, 2H. 7.2–7.6(m Ar.)

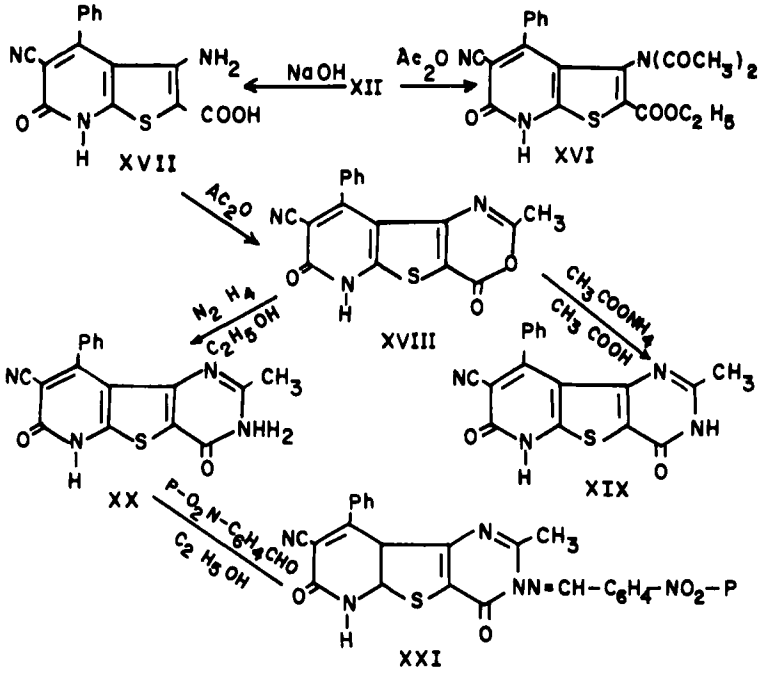
TABLE II—*Continued*

nd	M.P. [°C] (solvent)	Yield % colour	Molecular formula	Elemental analysis calculated/found					I.R. cm^{-1}	^1H NMI
				C	H	N	S	Br		
	168 (Ethanol)	57 Lemon	$C_{21}N_{17}N_3O_5S$	59.74 59.61	4.01 4.34	9.92 9.81	7.56 7.40	— —	3500, 3340(NH) 2240(CN), 1730 1690, 1650(C=O)	1.3–1.5(t, 3 CH_3) 2.3(s, 6H, $2CH_3$), 4. 4.5(9, 2H CH_2) 5.5(s, 1H, N 7.5–7.7 (m, 5H, Ar
	355 (Acetic acid)	68 Orange	$C_{15}H_9N_3O_3S$	57.87 57.58	2.89 3.10	13.50 13.69	10.28 10.54	— —	3500, 3400(NH_2) 3200(NH), 2220(CN), 1670(C=O).	—
	210 (Acetic acid)	67 White	$C_{17}H_9N_3O_3S$	60.89 70.56	2.68 2.91	12.53 12.44	9.55 9.37	— —	3320(NH), 2240(CN), 1740, 1650(C=O).	—
	352 (DMF)	81 Pale yellow	$C_{17}H_{10}N_4O_2S$	61.07 61.34	2.99 3.12	16.76 16.66	9.58 9.74	— —	3320, 3200(NH) 2240(CN), 1700(C=O)	2.7(s, 3H, C 7.3–7.7(s, 5 Ar.).
	310 (Ethanol)	72 Pale yellow	$C_{17}H_{11}N_5O_2S$	58.45 58.30	3.15 3.29	20.05 20.31	9.16 9.35	— —	3420, 3320(NH_2) 3240(NH), 2240(CN), 1670, 1650(C=O).	—
	285 (Acetic acid)	66 Yellow	$C_{24}H_{14}N_6O_4S$	59.75 59.60	2.90 2.67	17.42 17.29	6.63 6.87	— —	3340(NH), 2240(CN), 1670(C=O)	2.8(s, 3H, C 7.5–8.5(m, Ar.), 9.3(1H, CH).

region δ 5.7–8.6. Low ester or ketone carbonyl stretching frequencies around 1640–1680 cm^{-1} were found in the IR spectra of these compounds as a result of inter-amolecular hydrogen bonding with the ortho amino group.[12] The cyano groups of the synthesized compounds are collapsed to give one broad band.

Attempts to synthesize the hydrazide derivative of **XII** by reaction with hydrazine hydrate in ethanol or by fusion were unsuccessful. This led us to synthesize the acetyl derivative which facilitates the reaction of **XII** with hydrazine. Thus compound **XII** was refluxed in acetic anhydrid to give a product which was identified as *N*,*N*-diacetyl derivative (**XVI**) (c.f. Scheme 3 and Table II). But on treatment of **XVI** with hydrazine hydrate in ethanol for a few minutes compound **XII** was recovered. Hydrolysis of **XII** with 10% sodium hydroxide yielded after acidification the corresponding carboxylic acid **XVII** (c.f. Scheme 3 and Table II), which was reacted with acetic anhydride to give the xoazine derivative **XVIII** (c.f. Scheme 3 and Table II). The oxazine compound **XVIII** was reacted with ammonium acetate in acetic acid or with hydrazine hydrate in ethanol to give the pyrimidine derivatives **XIX**, **XX** respectively (c.f. Scheme 3 and Table II). *N*-Amino pyrimidine derivative **XX** was reacted with 4-nitro benzaldehyde to give the azomethine **XXI**.

Biological activity: As revealed from the results of agar diffusion tests the majority of the screened compounds showed antifungal activity and when the pyridine compounds were fused with the thieno rings a remarkable bactericidal activity was observed (c.f. Table III).



SCHEME 3

TABLE III

Bactericidal and fungicidal activities of selected synthesized compounds

Compound No.	Zone of inhibition* (nm)						
	S.a.	B.c.	S.sp.	K.sp.	P.n.	A.fl.	A.fu.
I	—	—	—	—	—	8	—
II	—	—	—	—	20	—	8
III	—	—	—	—	—	—	—
VIII	—	—	—	—	—	12	—
XII	—	12	—	—	—	—	—
XVI	—	—	12	—	—	—	—
$XIII_a$	—	10	—	—	18	—	—

* S.a. = Staphylococcus aureus; B.c. = Bacillus cereus; S.r. = Serrat rhodnii; K.p. = Klebsiella pneumaniae; P.n. = Penicillium nigricans; A.fl. = Aspergillus flavus; and A.fu. = Aspergillus fumigatus.

EXPERIMENTAL

Melting points are uncorrected. IR (KBr) spectra were recorded on Pye-Unicam infrared spectrophotometer and ^{1}H NMR spectra in DMSO-d_6 or $CDCl_3$ or TFA on a varian EM-390 spectrometer using TMS as internal standard, and chemical shifts are given as δ values. Analytical data were obtained from the microanalytical data unit at Cairo and Assiut University.

3,5-Dicyano-6-mercapto-4-phenyl pyridin-2(1H)-one (**I**) was prepared and isolated as reported earlier.[10]

Ethyl(3,5-dicyano-2-oxo-4-phenyl(1H)pyridin-6-ylthio)acetate (**II**). A mixture of **I** (2.5 g, 0.01 mol) and anhydrous sodium acetate (2 g) in ethanol (30 ml) was stirred with gentle heating for 10 minutes, then cooled and ethyl chloroacetate (1.1 ml, 0.01 mol) was added dropwise while stirring. The precipitate was collected by filtration and recrystallized (Table I).

(3,5-Dicyano-2-oxo-4-phenyl(1H)pyridin-6-ylthio)acetic acid hydrazide (**III**). A mixture of **II** (3.4 g, 0.01 mol) and hydrazine hydrate (0.5 ml, 0.01 mol) was refluxed in 30 ml ethanol for one hour. The reaction mixture was concentrated and poured into cold water. The precipitate was collected by filtration and recrystallized (Table I).

N-Acetyl(3,5-dicyano-2-oxo-4-phenyl (1H)pyridine-6-ylthio)acetic acid hydrazide (**IV**). A mixture of the hydrazide derivative (**III**) (3.2 g, 0.01 mol) and acetic acid (20 ml) was refluxed for one hour, then the reaction mixture was poured into 100 ml cold water. The solid which separated was collected by filtration and recrystallized (Table I).

N^1(3,5-Dicyano-2-oxo-4-phenyl(1H)pyridin-6-ylthiomethyl carbonyl)-N^4 phenyl semicarbazide (**V**) *and N^1(3,5-dicyano-2-oxo-4-phenyl(1H)pyridin-6-ylthiomethyl carbonyl) N^4-phenylthiosemicarbazide* (**VI**)*: General procedure.* A mixture of **III** (3.2 g, 0.01 mol) and phenyl isocyanate or phenylisothiocyanate (0.01 mol) was refluxed in 30 ml absolute ethanol for 1 hour. The precipitating product was collected while hot by filtration and recrystallized from the proper solvent (Table I).

Arylidene(3,5-dicyano-2-oxo-4-phenyl(1H)pyridin-6-ylthio)acetic acid hydrazones (**VII_{a-c}**). A mixture of hydrazide derivative **III** (3.2 g, 0.01 mol) and an aromatic aldehyde (0.01 mol) in 30 ml ethanol was refluxed for one hour. The precipitate formed was collected while hot by filtration and recrystallized (Table I).

6(3',5'-Dimethylpyrazol-1'-yl)carbonyl methyl thio 3,5-dicyano-4-phenylpyridin-2-(1H)-one (**VIII**). A mixture of the hydrazide derivative **III** (3.2 g, 0.01 mol) and acetyl acetone (1 ml, 0.01 mol) in 30 ml ethanol was refluxed for five hours. The reaction mixture was concentrated and the precipitate was collected by filtration and recrystallized (Table I).

N-Aryl(3,5-dicyano-2-oxo-4-phenyl(1H)pyridin-6-ylthio)acetamides (**IX_{a-c}**)*; 6-acetylmethylthio-3,5-dicyano-4-phenylpyridin-2(1H)-one* (**X**) *and 6-arylcarbonyl methylthio-3,5-dicyano-4-phenylpyridin-2(1H)-ones* (**XI_{a-c}**)*: General procedure.* A mixture of **I** (2.5, 0.01 mol), and anhydrous sodium acetate was

stirred for five minutes in 30 ml ethanol, then chloroanilide (0.01 mol); bromo acetone (0.01 mol) or phenacyl bromide (0.01 mol) was added while stirring; the reaction mixture was stirred for 30 minutes. The precipitated products were collected by filtration and recrystallized (Table II).

2-Substituted-3-amino-5-cyano-4-phenyl thieno[2,3-b]pyridin-6(7H)-ones (**XII–XV**)*: General procedure.* To a solution of **II** or **IX–XII** (0.01 mol) in 30 ml absolute ethanol, 2 ml of ethanolic sodium ethoxide was added dropwise while stirring; the reaction mixture was stirred for 30 minutes after which the precipitated products were collected by filtration and recrystallized (Table II).

2-Carboethoxy-5-cyano 3-N,N-diacetylamino-4-phenylthieno[2,3-b]pyridin-6(7H)one (**XVI**). A mixture of **XII** (3.3 g 0.01 mol) and acetic anhydride (20 ml) was refluxed for five hours. The reaction mixture was allowed to cool, then poured into ice/water mixture and the precipitate thus formed was collected by filtration and recrystallized (Table II).

3-Amino-2-carboxy-5-cyano-4-phenylthieno[2,3-b]pyridin-6(7H)-one (**XVII**). A mixture of **XII** (3.3 g, 0.01 mol) and alcoholic sodium hydroxide (50 ml 10%) was refluxed for 30 minutes. The sodium salt of **XVII** was formed as a precipitate and filtered off. The sodium salt was dissolved in 30 ml H_2O and acidified with dilute HCl, the solid free acid which separated was collected by filtration and recrystallized (Table II).

8-Cyano-6(H)-2-methyl-9-phenyl(1H)pyrido[3',2':4,5]thieno[3,2-d][3,1]oxazin-4,7-dione (**XVIII**). A mixture of **XVII** (3.1 g, 0.01 mol) and acetic anhydride (20 ml) was refluxed for 1 hour. The reaction mixture was allowed to cool and the solid obtained was collected by filtration and recrystallized (Table II).

8-Cyano-2-methyl-9-phenyl-pyrido[3',2':4,5]thieno[3,2-d]pyrimidin-4,7-dione (**XIX**). A mixture of oxazino derivative (**XVIII**) (3.5 g, 0.01 mol) and 10 g ammonium acetate in 20 ml acetic acid was refluxed for 15 minutes, the precipitate thus formed was collected while hot by filtration, and recrystallized (Table II).

3-Amino-8-cyano-2-methyl-9-phenyl-pyrido[3',2':4,5]thieno[3,2-d]pyrimidin-4,7-dione (**XX**). A mixture of oxazine derivative (**XVIII**) (3.3 g, 0.01 mol) and hydrazine hydrate (0.5 ml, 0.01 mol) in 20 ml ethanol was refluxed for one hour, then cooled and the precipitate was collected by filtration and recrystallized (Table II).

8-Cyano-2-methyl 3-(p-nitrobenzlidene amino)-9-phenyl pyrido[3',2':4,5]thieno[3,2-d]pyrimidin-4-7-dione (**XXI**). A mixture of (**XX**) (3.4 g, 0.01 mol) and 4-nitrobenzaldhyde (1.5 g, 0.01 mol) in 20 ml ethanol in presence of few drops of piperidine as a catalyst was refluxed for two hours, the precipitate thus formed was collected while hot by filtration and recrystallized (Table II).

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