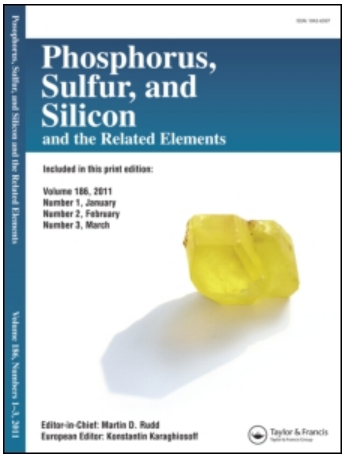

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SYNTHESIS AND REACTIONS OF SOME THIENOPYRIDINE DERIVATIVES

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SYNTHESIS AND REACTIONS OF SOME THIENOPYRIDINE DERIVATIVES

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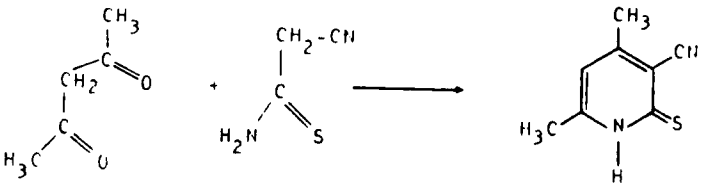
Substituted thieno[2,3-b]pyridines (**VIII–XII**) were prepared by ring closure of the corresponding *S*-alkylated derivatives (**II–VI**). Thieno[2,3-*b*]pyridine-2-carbohydrazide **XIII** was interacted with some reagents afforded the expected pyridothienopyrimidines (**XIV–XVI**). Also, the carboazide **XVII** undergo Curtius rearrangement giving imidazolothienopyridine (**XVIII**). The carboxamide derivatives (**X–XII**) interacted with CS_2 giving pyridothienopyrimidines (**XX–XXII**), while interaction with nitrous acid, pyridothienotriazines (**XXIII–XXV**) were produced.

Key words: Synthesis, thienopyridine, pyridothienopyrimidine, pyridothienotriazine.

INTRODUCTION

Unlike their benzene counterparts, thienopyridines do not occur widely in nature. Many of the available thienopyridines have been evaluated pharmacologically and have been found to show activity against dibetes mellitus, as analgesics and antiinflammants.[1–4]

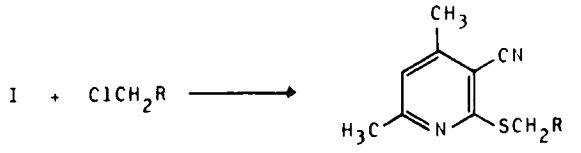
Considering the foregoing benefits we aimed herein to synthesize some unreported thienopyridine derivatives for a biological interest. Thus, the key intermediate compound, 3-cyano-4,6-dimethyl pyridine-2(1H-)thione(1)[5] was prepared for exploration of the thiol group for synthetic building blocks as follows:



(1)

The alkylation of compound (**I**) with some alkylating agents in ethanol in presence of sodium acetate was carried out following the procedure of Krauze *et al.*[6] giving the *S*-alkylated products (**II–VI**).

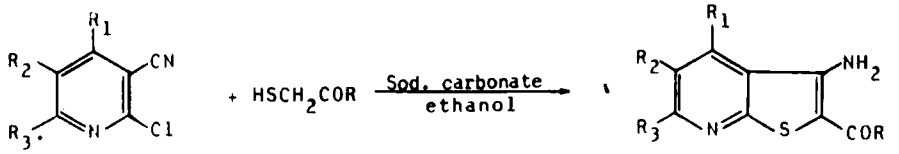
The structure of compounds **II–VI** was supported by analysis and their IR spectra. The IR spectra showed bands at 2200–2250 cm^{-1} (C≡N), at 2260 cm^{-1} for the other (C≡N) group of compound (**II**) and at 1750 cm^{-1} for the C=O



II, R=CN
III, R=COOEt
IV, R=CONHC$_6$H$_5$
V, R=CONH- 
VI, R=CONH- 

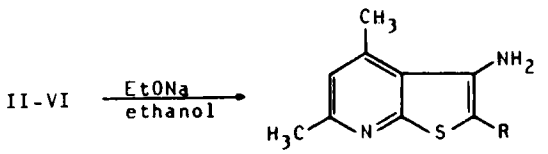
group of compound **III**. Compounds **IV–VI** showed bands at 3100–3300 cm^{-1} (NH group) and at 1660–1690 cm^{-1} (C=O group).

Krauze *et al.*[6] cyclized the intermediate compound from the alkylation of **I** (phenyl group instead of methyl) to the corresponding thienopyridine using sodium methoxide. However, the substituted thienopyridine (**VII**) *has been synthesized* by Skvedov *et al.*[7] by the following reaction.



(VII)

In our case, the target thienopyridines (**VIII–XII**) were synthesized by ring closure of the intermediates (**II–VI**) in ethanol in presence of sodium ethoxide as follows:

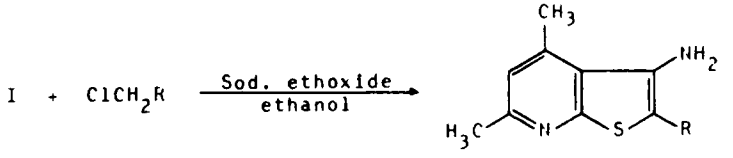


VIII, R=CN
IX, R=COOEt
X, R=CONHC$_6$H$_5$
XI, R=CONH- 
XII, R=CONH- 

The structure of compounds **VIII–XII** was confirmed by the correct elemental analysis, IR and ^{1}H NMR spectra. The IR spectra of compounds **VIII–XII**

showed the absence of bands characteristic for (C≡N) group and the appearance of a bands at 3500–3320 cm^{-1} for (NH_2) group. The ^1H NMR of **IX** in $CDCl_3$ showed the following signals at δ 1.3–1.45 (t, 3H, CH_3 of ester group), δ 2.55, δ 2.65 (2s, 6H, $2CH_3$), δ 4.15–4.40 (q, 2H, CH_2 of ester group), δ 6.05 (s, 2H, NH_2) and at 6.7 (S, 1H, CH-pyridine). Compounds **X** in $CDCl_3$ showed signals at δ 2.5, δ 2.7 (2s, 6H, $2CH_3$); δ 4.6 (s, 2H, NH_2); δ 6.75 (s, 1H, CH-pyridine); δ 6.95–7.55 (m, 5H, Ar—H) and δ 7.9 (s, 1H, NH).

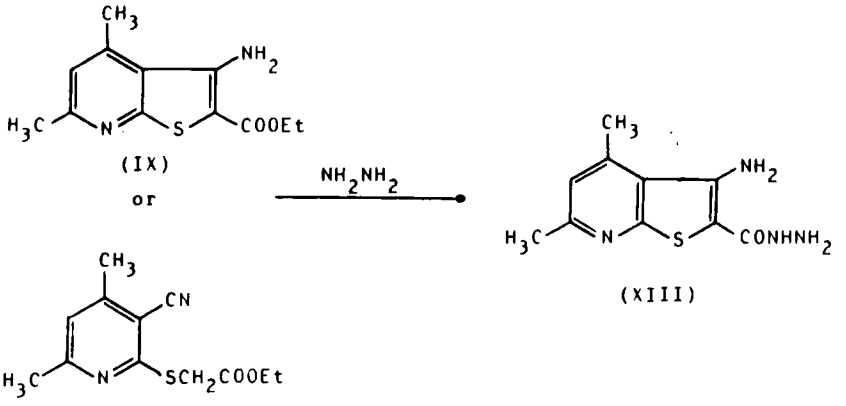
Further support for the foregoing structure of the thienopyridines (**VIII–XII**) was obtained from an alternative one-step synthesis. Thus, when compound (**I**) was allowed to react with the alkylating agents in presence of sodium ethoxide, products **VIII–XII** were isolated in good yield.



(VIII-XII)

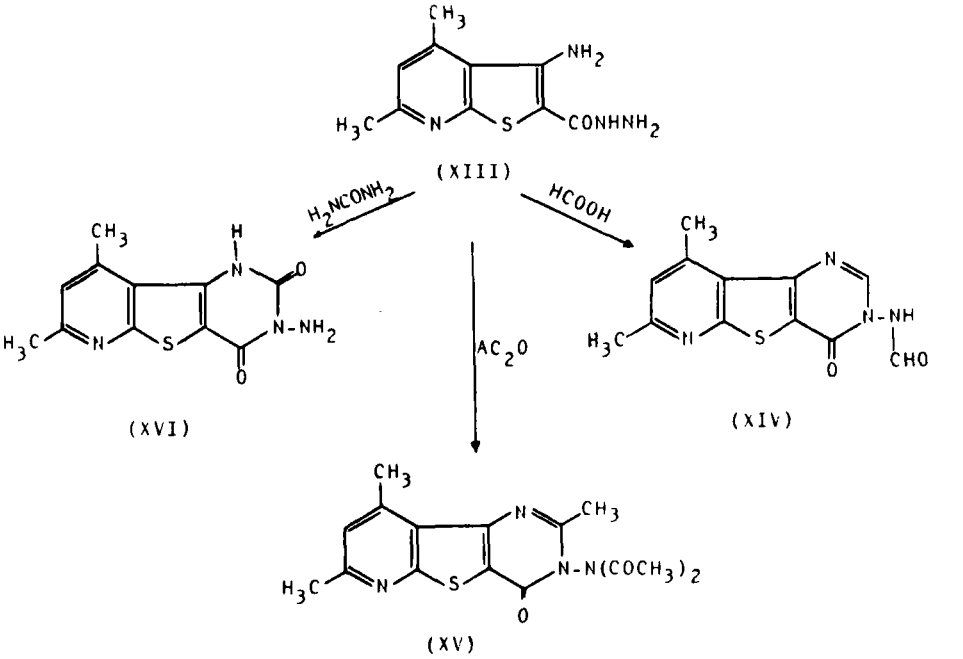
The identity of the two products obtained from the different routes was indicated through their m.p.; m.m.p.; TLC and superimpossible IR spectra.

The above finding prompted our interest to survey the chemistry of some *o*-disubstituted thienopyridines and their uses as precursers for synthesis of some interesting tricyclic compounds. Thus, when the thienopyridine *o*-amino carboxylate (**IX**) and/or compound (**III**) interacted with hydrazine hydrate, the hydrazide (**XIII**) was obtained in good yield.

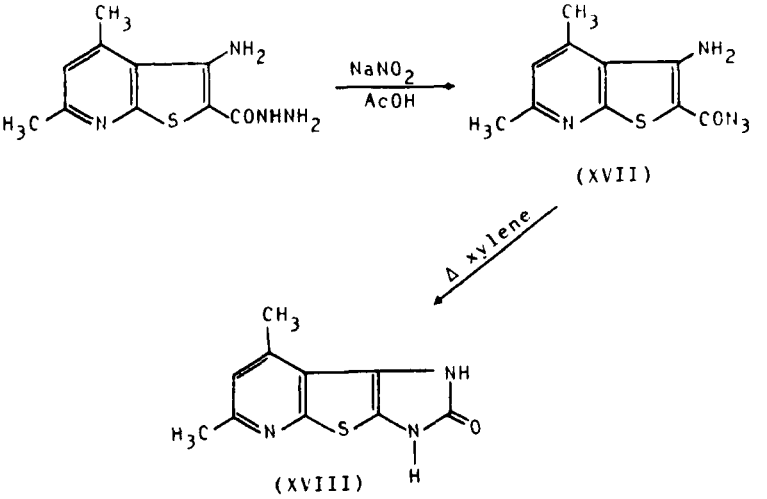


Interaction of hydrazide **XIII** with some reagents namely, formic acid, acetic anhydride and urea gave the tricyclic compounds (**XIV–XVI**).

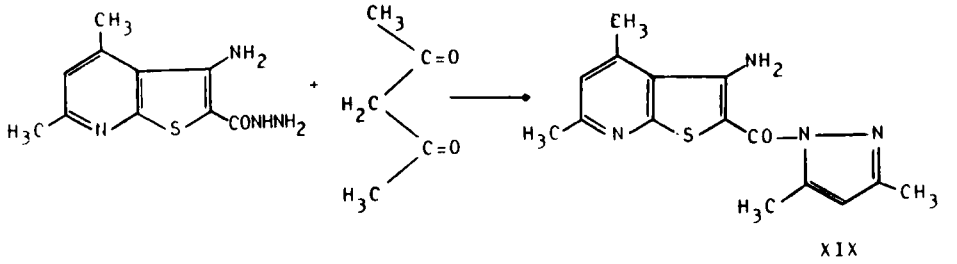
The structure of compounds **XIV–XVI** was confirmed by their correct elemental analysis, IR and ^1H-NMR spectra. The IR spectra showed bands at



3180 cm^{-1} (C=O group) (compound **XIV**); at 1690, 1740 cm^{-1} (C=O group) (compound **XV**); at 3500–2900 cm^{-1} (NH_2 and NH groups) and at 1680, 1740 cm^{-1} (C=O group) (compound **XVI**). The ^1H NMR of XIV in CF_3COOH showed signals at δ 3.00, δ 3.30 (2s, 6H, $2CH_3$); δ 7.7 (s, 1H, CH pyridine); δ 8.45 (s, 1H, CH pyrimidine), δ 8.7 (s, 1H, CH formyl), and at δ 9.95 (s, 1H, NH). The ^1H NMR of **XV** in $CDCl_3$ showed signals at δ 2.4 (s, 6H, $N(COCH_3)_2$), δ 2.5, δ 2.65, δ 2.90 (3s, 9H, $3CH_3$) and at δ 7.0 (s, 1H, CH pyridine). However, interaction with nitrous acid gave the azide (**XVII**) which easily cyclized when heated in xylene giving (**XVIII**).

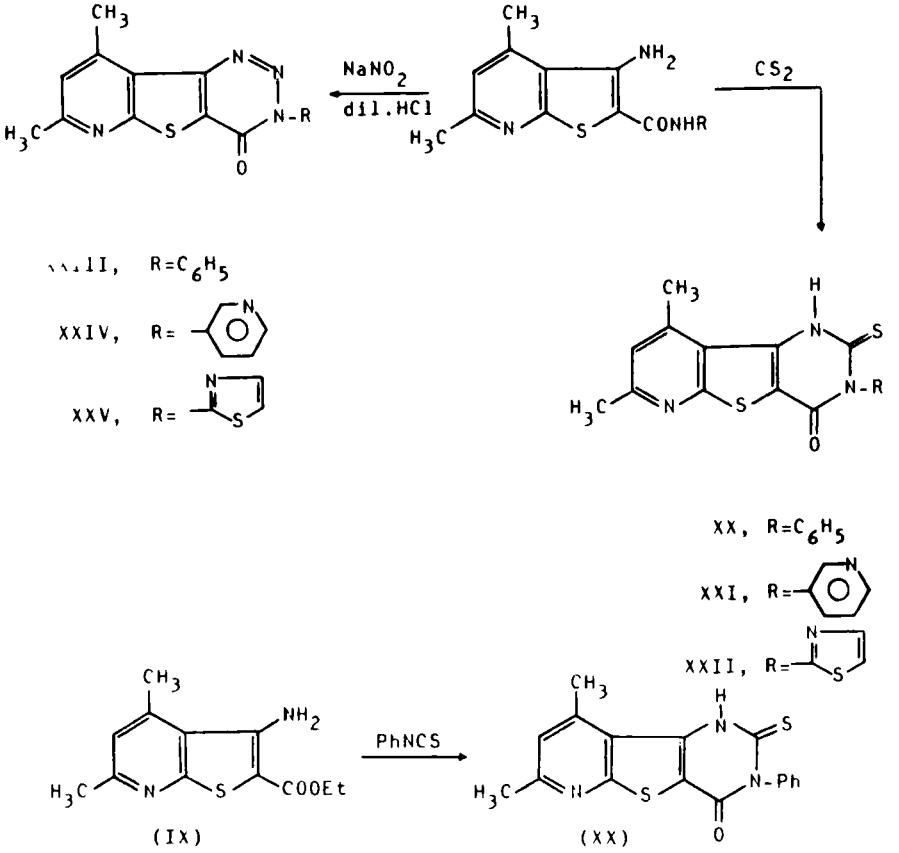


On the other hand, acetylacetone condensed with the terminal hydrazide group giving a pyrazole structure (**XIX**).



XIX

The structure of compounds **XVII–XIX** was established from their correct elemental analysis, IR, and ^{1}H NMR spectra. The IR spectra showed bands at 3480–3330 cm^{-1} (NH_2) group and at 2120 cm^{-1} (CON_3) group (compound **XVII**); at 3500–3300 cm^{-1} (NH) group and at 1700 cm^{-1} (C=O) group (compound **XVIII**); at 3540–3340 cm^{-1} (NH_2) group; at 1640 cm^{-1} (C=O) group (compound **XIX**). The ^{1}H NMR of **XVIII** in DMSO-d_6 showed signals at δ 2.45, δ 2.55 (2s, 6H, $2CH_3$); δ 6.95 (s, 1H, CH pyridine).



XXIII, R=C_6H_5

XXIV, R=

XXV, R=

XX, R=C_6H_5

XXI, R=

XXII, R=

(IX) (XX)

A further group of tricyclic compounds was synthesized from the corresponding amides. Thus, when the amides (**XX–XXII**) were caused to interact with carbon disulphide and or nitrous acid they gave the corresponding tricyclic compounds (**XXIII–XXVII**), respectively.

A chemical confirmation for the structure of compound **XX** was obtained through its synthesis from the reaction of compound **IX** with phenyl isothiocyanate.

It must be pointed out that, the synthesis of compounds (**XX**) from the reaction of **XI** with CS_2 is a comfortable way for the introduction of different substituents in the third built ring.

The structure of compounds **XX–XXIV** was confirmed by their elemental analysis and by their spectral analysis. The IR spectra of **XX–XXII** showed absorption bands at 3300–3250 cm^{-1} (NH) group, and at 1200 cm^{-1} (C=S) group. ^1H NMR of **XX** in $CDCl_3$ showed the following signals, δ 2.65, δ 2.85 (2s, 6H, $2CH_3$), δ 7.05 (s, 1H, CH pyridine), and δ 7.20–7.5 (m, 6H, Ar—H and NH). IR of **XXIII–XV** showed the absence of band characteristic for (NH_2) and showed a band at 11680–1690 cm^{-1} (C=O) group.

EXPERIMENTAL

Melting points are uncorrected and were determined on a Mel-Temp II melting point apparatus. IR spectra were recorded on Pye-Unicam SP 3-100 and Perkin–Elmer 599 B spectrophotometer using KBr Wafer technique. ^1H NMR spectra were recorded on a Varian EM-390 90 MHz NMR spectrometer in the suitable deutrated solvents, using TMS as internal standard. Elemental analysis were determined on a Perkin–Elmer 240 C micro analyser.

Alkylation of 3-cyano-4,6-dimethyl pyridine-2(1H)thione: General procedure. A mixture of 3-cyano-4,6-dimethyl-2(1H)thione(I) (0.01 mole), alkylating agent (0.01 mole) and sodium acetate (2 gm) in ethanol (30 ml) was refluxed for $\frac{1}{2}$hr. The precipitated solid which formed on cooling or dilution with water, was filtered off, washed with water and dried. The physical constants of compounds **II–VI** are listed in Table I.

Cyclization of 2-alkylthio-3-cyano-4,6-dimethyl pyridine (**II–VI**)*: General procedure.* To a solution of appropriate 2-alkylthio-3-cyano-4,6-dimethyl pyridine (**II–VI**) (0.01 mole) in 30 ml of ethanol, a few drops of ethanolic sodium ethoxide solution were added. The solution was refluxed for 15 minutes and left to cool. The solid obtained was filtered and recrystallized from ethanol. The physical properties of compounds **VIII–XII** are represented in Table I.

3-Amino-4,6-dimethylthieno[2,3-b]pyridine-2-carbohydrazide (**XIII**). Method A: A mixture of **IX** (0.01 mole) and hydrazine hydrate (3 ml) was refluxed for 2 hrs., then ethanol (20 ml) was added and the mixture was boiled and filtered while hot. The solid which formed was filtered off, washed several times with hot ethanol and recrystallized from pyridine to give yellow crystals in 32% yield, m.p. 218–20°C.

Method B: A mixture of compound **III** (0.01 mole) and hydrazine hydrate (3 ml) was refluxed on a water bath for 2 hrs. The solid product was collected and recrystallized from pyridine to give yellow crystals in 85% yield, m.p. 218–20°C.

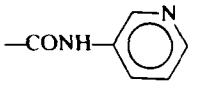
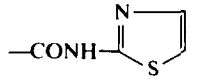
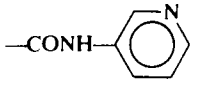
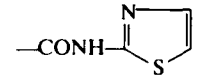
Anal. Calcd. For: $C_{10}H_{12}N_4OS$: C, 50.83; H, 5.12; N, 23.71; S, 13.57%
Found: C, 51.15; H, 4.94; N, 23.70; S, 13.52%.

3-Formyl-7,9-dimethylpyrido[3′,2′:4,5]thieno[3,2-d]pyrimidine-4-(3H)-one (**XIV**). A sample of compound **XIII** (0.01 mole) in formic acid (10 ml) was refluxed for 4 hrs, then allowed to cool and diluted with water. The solid product was collected and recrystallized from ethanol to give white crystals in 86% yield, m.p. 253–5°C.

Anal. Calcd. For: $C_{12}H_{10}N_4O_2S$: C, 52.55; H, 3.67; N, 20.43; S, 11.69%
Found: C, 52.27; H, 3.61; N, 20.78; S, 11.50%.

TABLE I

Physical constants of compounds **II–XII**:

Compd. No.	R	M.P. C	Yield %	Molecular formula	Analysis Calcd. (Found)(%) C	H	N	S
II	-CN	120–1	84	$C_{10}H_9N_3S$	59.09 (59.60)	4.46 (4.55)	20.67 (21.00)	15.77 (16.00)
III	-COOEt	53–5	80	$C_{12}H_{14}N_2O_2S$	57.58 (58.20)	5.64 (5.00)	11.19 (11.25)	12.81 (12.45)
IV	$-CONHC_6H_5$	176–8	67	$C_{16}H_{15}N_3OS$	64.62 (64.69)	5.08 (5.44)	14.13 (13.80)	10.78 (11.00)
V		204–5	64	$C_{15}H_{14}N_4OS$	60.38 (60.00)	4.73 (4.55)	18.78 (19.00)	10.75 (10.98)
VI		235–7	66	$C_{13}H_{12}N_4OS_2$	51.30 (50.90)	3.97 (4.25)	18.41 (18.10)	21.07 (21.30)
VIII	-CN	213–5	92	$C_{10}H_9N_3S$	59.09 (59.30)	4.46 (4.70)	20.67 (20.70)	15.77 (16.00)
IX	-COOEt	155–7	95	$C_{12}H_{14}N_2O_2S$	57.58 (57.30)	5.64 (5.90)	11.19 (10.80)	12.81 (13.10)
X	-CONHPh	223–5	86	$C_{16}H_{15}N_3OS$	64.62 (64.25)	5.08 (5.40)	14.13 (13.80)	10.78 (11.00)
XI		254–6	85	$C_{15}H_{14}N_4OS$	60.38 (59.98)	4.73 (5.00)	18.78 (18.55)	10.75 (10.50)
XII		320	80	$C_{13}H_{12}N_4OS_2$	51.30 (51.40)	3.97 (4.20)	18.41 (18.05)	21.07 (20.80)

3-Diacetylamino-2, 7, 9-trimethylpyrido[3′,2′:4,5]thieno[3,2-d]-pyrimidine-4(3H)-one (**XV**). A sample of compound **XIII** (0.01 mole) in acetic anhydride (10 ml) was refluxed for 3 hrs, the solid product which formed on cooling was collected and recrystallized from ethanol to give white needles in 69% yield, m.p. 215–17°C.

Anal. Calcd. For: $C_{16}H_{16}N_4O_3S$: C, 55.80; H, 4.68; N, 16.27; S, 9.31%
Found: C, 55.48; H, 4.79; N, 15.89; S, 9.50%.

3-Amino-7, 9-dimethylpyrido[3′,2′:4,5]thieno[3,2-d]pyrimidine-2,4-(1H,3H)-dione(**XVI**). A mixture of compound **XIII** (0.002 mole) and urea (0.005 mole) was reflexed in decaline (20 ml) for 3 hrs. The solid product was collected, washed with petrolium ether and recrystallized from DMSO-H_2O to give a buff powder in 72% yield, m.p. 350°C.

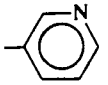
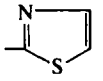
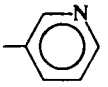
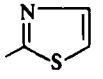
Anal. Calcd. For: $C_{11}H_{10}N_4O_2S$: C, 50.37; H, 3.84; N, 21.36; S, 12.22%.
Found: C, 50.59; H, 3.55; N, 21.10; S, 12.53%.

3-Amino-4, 6-dimethylthieno[2,3-b]pyridine-2-carbonylazide (**XVII**). Sodium nitrite solution (0.01 mole in 7 ml H_2O) was added to a solution of compound **XIII** (0.002 mole) in acetic acid (10 ml) at room temperature during 5 minutes with stirring. The solid product was filtered and recrystallized from ethanol to give yellow needles in 96% yield, m.p. 170°C dec.

Anal. Calcd. For: $C_{10}H_9N_5OS$: C, 48.57; H, 3.67; N, 28.32; S, 12.97%.
Found: C, 48.38; H, 3.57; N, 28.11; S, 13.10%.

TABLE II

Physical constants of compound **XX–XXV**

Compd. No.	R	M.P. °C	Yield %	Molecular formula	Analysis Calcd./(Found)(%) C	H	N	S
XX	$-C_6H_5$	263–5	88	$C_{17}H_{13}N_3OS_2$	60.16 (59.94)	3.86 (3.48)	12.38 (12.52)	18.89 (19.10)
XXI		310–12	74	$C_{16}H_{12}N_4OS_2$	56.45 (56.31)	3.55 (3.42)	16.46 (16.24)	18.84 (18.50)
XXII		330–2	72	$C_{14}H_{10}N_4OS_3$	48.54 (48.83)	2.91 (3.11)	16.17 (16.30)	27.76 (28.00)
XXIII	$-C_6H_5$	230–2	96	$C_{16}H_{12}N_4OS$	62.32 (61.95)	3.92 (4.15)	18.17 (18.49)	10.40 (10.50)
XXIV		243–5	90	$C_{15}H_{11}N_5OS$	58.24 (58.49)	3.58 (3.25)	22.64 (22.22)	10.36 (10.50)
XXV		175–7	87	$C_{13}H_9N_5OS$	49.51 (49.28)	2.88 (2.95)	22.21 (22.00)	20.33 (20.13)

Rearrangement of **XVII** *to form 4,6-dimethyl-1H-imidazolo[4′,5′:4,5]-thieno[2,3-b]pyridin-2(3H)-one* (**XVIII**). A sample of compound **XVII** (0.5 gm) was refluxed for ½hr. in xylene (20 ml). The solid product was collected and washed several times with hot xylene to give compound (**XVIII**) in 90% yield, m.p. 350°C.

Anal. Calcd. For $C_{10}H_9N_3OS$: C, 54.78; H, 4.14; N, 19.16; S, 14.62%.
Found: C, 54.00; H, 4.10; N, 18.90; S, 14.50%.

1-[3-Amino-4,6-dimethylthieno[2,3-b]pyridine-2-ylcarbonyl]-3,5-dimethylpyrazole (**XIX**): A mixture of compound **XIII** (0.002 mole) and acetylacetone (0.004 mole) was refluxed in ethanol for 4 hrs. On cooling the precipitated solid product was collected and recrystallized from ethanol to give yellow crystals in 68% yield, m.p. 240–2°C.

Anal. Calcd. For: $C_{15}H_{16}N_4OS$: C, 59.98; H, 5.37; N, 18.65; S, 10.67%.
Found: C, 60.20; H, 5.66; N, 18.54; S, 10.68%.

7,9-Dimethyl-3-phenyl/(3-pyridyl) or/(2-thiazolyl)-2-thiopyrido[3′,2′:4,5]thieno[3,2-d]pyrimidine-2,4(1H,3H)-dione (**XXIII–XXV**): A mixture of compound (**X** and/or **XII**) (0.002 mole) and carbon disulfide (2 ml) in dry pyridine (30 ml) was heated on a water bath for 6 hrs. The solid product which precipitated on cooling was collected and recrystallized from pyridine. The physical constants of compounds (**XXIII–XXV**) are represented in Table II.

Reaction of phenyl isothiocyanate with compound (**IX**). A mixture of compound (**IX**) (0.01 mole) and phenyl isothiocyanate (0.01 mole) in pyridine (30 ml) was refluxed for 8 hrs, allowed to cool, diluted with water and acidified with acetic acid. The solid product was collected and recrystallized from benzene, to give compound **XXIII** in 28% yield, m.p. 263–5°C.

Reaction of N-substituted-3-amino-4,6-dimethyl[2,3-b]pyridine-2-carboxamides. Sodium nitrite solution (0.01 mole in 7 ml H_2O) was added to a solution of compound (**X–XII**) (0.002 mole) in conc. HCl (5 ml) at 0°C during 5 minutes with stirring. The solid product was collected and recrystallized from acetic acid to give compounds **XX–XXII**. The physical constants of compounds **XX–XXII** are listed in Table II.

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