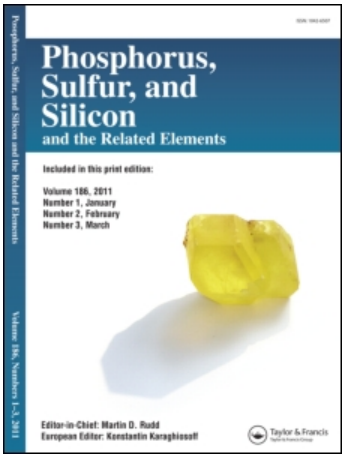

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STUDIES WITH POLYFUNCTIONALLY SUBSTITUTED HETEROAROMATICS: NEW ROUTES FOR SYNTHESIS OF BENZOAZINES

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STUDIES WITH POLYFUNCTIONALLY SUBSTITUTED HETEROAROMATICS: NEW ROUTES FOR SYNTHESIS OF BENZOAZINES

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Pyridazine (**I**) reacts with dimethyl acetylenedicarboxylate and with N-phenyl-maleimide yielding phthalazine (**II**) and pyrrolophthalazine (**III**), respectively. Pyridine **IV** reacts with benzylidene malononitrile to give compound **VI**. Compounds **VIa–c** could be successfully converted into the isoquinolines **XIa–c** on treatment with acrylonitrile. In contrast to the behavior of arylidene malononitrile, compound **IV** react with N-phenylmaleimide to yield the pyrroloisoquinoline **XIII**. Similarly, the reaction of compound **IV** with each of tetracyanoethylene and dimethyl acetylenedicarboxylate gave compounds **XIV** and **XV** respectively.

Key words: Phthalazine, pyrrolophthalazine, isoquinoline, pyrroloisoquinoline, pyridothienopyridine.

Polyfunctionally substituted heteroaromatics are interesting as potential pharmaceuticals[1–4] and as intermediates in dye industry.[5–8] Generally benzoazines are prepared via cyclization of appropriate functionally substituted benzene derivatives. These synthetic approaches can be adopted only with difficulty for synthesis of polyfunctionally benzoazines as polysubstituted benzene are not readily obtainable compounds. For this reason Elnagdi *et al.*[9,10] have developed new synthesis of benzoazines utilizing alkylazinyl-carbonitriles as starting materials. Now we are interested to see if reactions of this type can be adopted to constitute a new general route for synthesis of benzoazines.

The pyridazine **I** reacts with dimethyl acetylenedicarboxylate to yield a 1:1 adduct which may be assigned structure **II** and which is assumed to be formed via intermediacy of a nonisolable Michael adduct. It seems that the cyclization of the Michael adduct occurs simultaneously, driven by aromaticity of the resulting ring. Structure **II** could be established for the product based on the IR spectra which revealed the absence of a CN-band at 2220 cm^{-1} and the appearance of an amino function at 3420–3310 cm^{-1}. Similar to its behavior towards dimethyl acetylenedicarboxylate, compound **I** also reacts with N-phenylmaleimide yielding the pyrrolophthalazine **III**.

In contrast to reported formation of isoquinoline,[11] on treatment of **IV** with benzylidenemalononitrile only monoarylidene derivatives which may be formulated as **V** or isomeric **VI** were formed. Structure **VI** was established based on ^{1}H-nmr analysis which revealed the appearance of the methyl function at C-4. Moreover the IR spectra revealed a CN group absorption at exactly the same value (2220 cm^{-1}) observed for this function in starting compound **IV**. If the reaction product was compound **V**, one would expect this band to shift to a longer wavelength as a

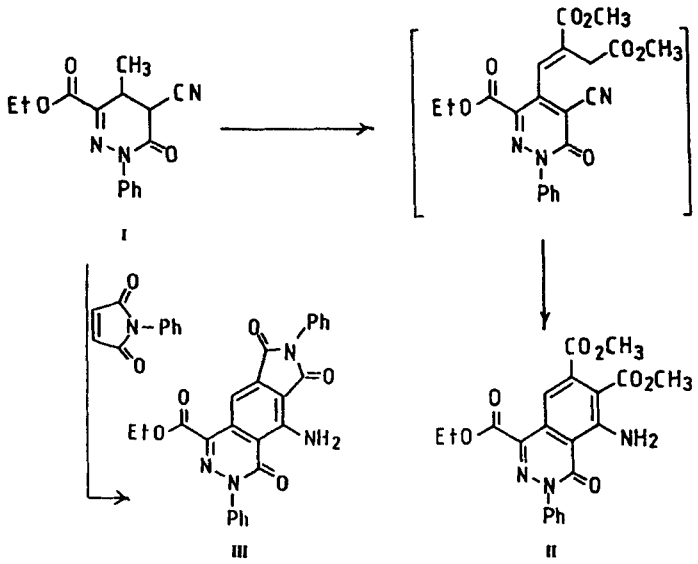


TABLE I

Comp* no.	M.P. °C	Yield %	Ar	Formula (M.W.)	Analysis Found (Calcd.) C	H	N	S	Mass m/z (M^+)
VIa	120	60	C_6H_5	$C_{15}H_{12}N_2S$ (252)	71.23 (71.42)	4.60 (4.76)	11.02 (11.11)	12.61 (12.69)	252
VIb	260	60	$C_6H_4OCH_3$-p	$C_{16}H_{14}N_2OS$ (282)	67.98 (68.08)	4.92 (4.96)	9.87 (9.92)	11.27 (11.34)	282
VIc	156	56	C_6H_4Cl-p	$C_{15}H_{11}N_2SCl$ (286.5)	62.61 (62.82)	3.75 (3.83)	9.68 (9.77)	11.09 (11.16)	286

*Ir spectra (KBr) for VIa-c display absorption bands around 3380 (NH), 2919 (CH_3), 2220 (CN), 1640 (C=C), 1260 cm^{-1} (C=S).

• ^{1}H-NMR: (ppm) for VIa = 2.6 (s, H, CH_3), 7.8 (m, H, aroamtic protons and ethylenic protons).

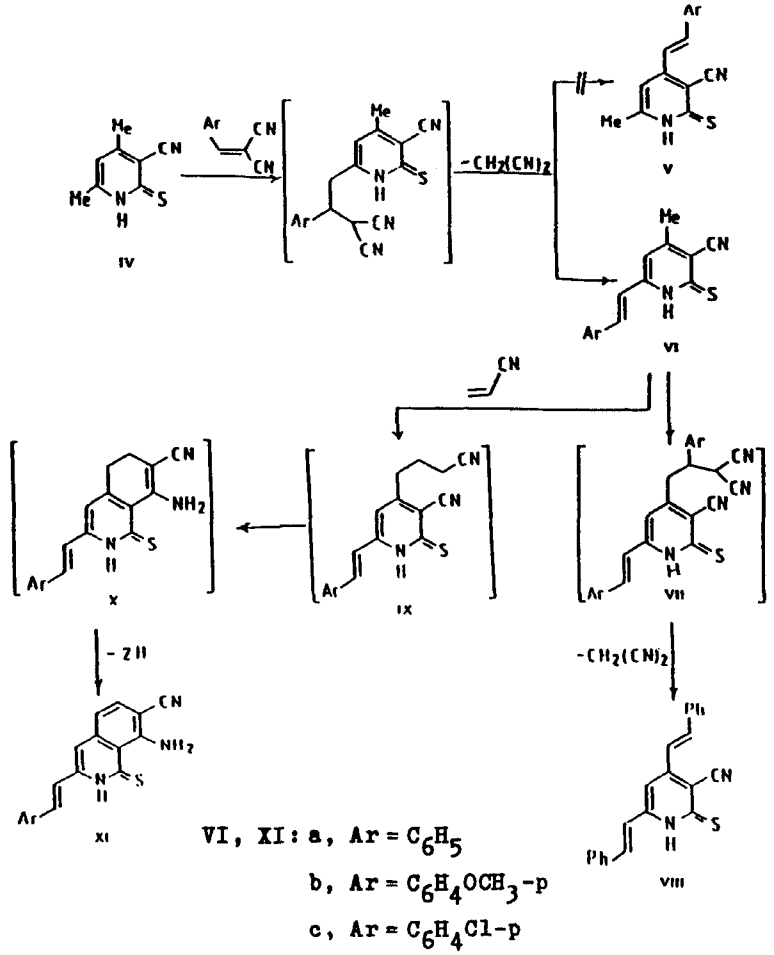
result of extra conjugation. Attempted addition of another molecule of benzylidenemalononitrile to **VI** resulted only in the formation of dibenzylidene derivative, **VIII**, which was assumed to occur via addition of the C-4 methyl function to the activated double bond and subsequent elimination of malononitrile. Compounds **VIa–c** could be successfully converted into the isoquinoline **XIa–c** on treatment with acrylonitrile. This product is assumed to be formed via addition of C-4 methyl function in **VIa–c** to the activated double bond of acrylonitrile yielding Michael adduct **IXa–c** which is readily cyclized into **Xa–c** then aromatized into **XIa–c**.

TABLE II

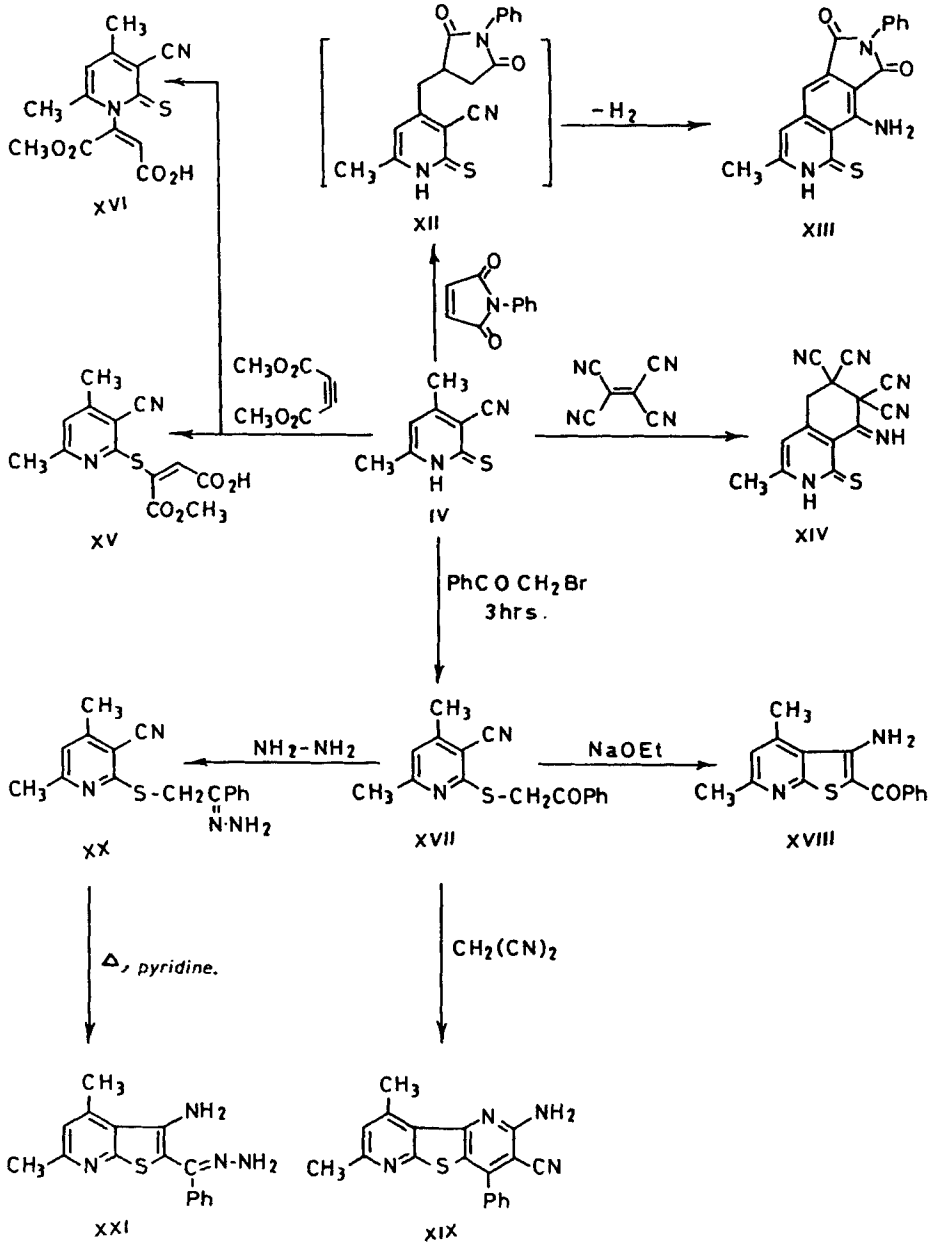
8-Amino-1,2-dihydro-3-styryl-1-thioxoisoquinoline-7-carbonitrile (**XIa–c**)

Comp* no.	M.P. °C	Yield %	Ar	Formula (M.W.)	Analysis Found (Calcd.) C	H	N	S	Mass m/z (M^+)
XIa	170	65	C_6H_5	$C_{18}H_{13}N_3S$ (303)	71.01 (71.28)	4.15 (4.29)	13.67 (13.86)	10.43 (10.56)	306
XIb	150	62	$C_6H_4OCH_3$-p	$C_{19}H_{15}N_3OS$ (333)	68.21 (68.46)	4.37 (4.50)	12.53 (12.61)	9.58 (9.60)	335
XIc	188	50	C_6H_4Cl-p	$C_{18}H_{12}N_3SCl$ (337.5)	63.81 (64.00)	3.43 (3.55)	12.30 (12.44)	9.42 (9.48)	340

*Ir spectra (KBr) for XIa-c display absorption bands around 3440-3335 (NH_2), 2205 (CN), 3040 (CH aromatic), 1628 (C=C), 1243 cm^{-1} (C=S).



In contrast to its behavior towards arylidenemalononitrile, compound **IV** reacts with N-phenylmaleimide to yield the pyrroloisoquinoline, **XIII**, via the intermediacy of **XII**. Structure **XIII** could be established by IR spectra which revealed an absence of a CN band and the appearance of the NH_2 group vibration. Similarly, compound **IV** reacted with tetracyanoethylene to yield **XIV**. Reaction of **IV** with dimethyl acetylenedicarboxylate afforded a product of molecular formula $C_{13}H_{12}N_2O_4S$. ^{1}H-nmr analysis of this product revealed that the two methyl function at C_4 and C_6



were not involved in the reaction. Thus, we have assumed either structure **XV** which may result from addition of the sulfur nucleophile to the activated triple bond and subsequent hydrolysis catalyzed by the ring nitrogen lone pair or structure **XVI** which may result from addition of the nitrogen nucleophilic triple bond and subsequent hydrolysis catalyzed by the sulfur atom lone pair.

The pyridine **IV** reacts with phenacyl bromide to yield the S-alkylpyridine **XVII** which could be cyclized into thienopyridine **XVIII** on continued reflux with sodium ethoxide. Compound **XVIII** could be directly obtained on continued reflux of **IV** with phenacyl bromide in pyridine solution.

Compound **XVII** afforded the pyridothienopyridine **XIX** on treatment with malononitrile. Attempted cyclization of **XVII** into **XXI** via treatment with hydrazine hydrate afforded the hydrazone derivative **XX** which could be cyclized into **XXI** on continued reflux in pyridine. Compound **XXI** could be directly obtained via condensation of **XVIII** with hydrazine hydrate.

EXPERIMENTAL

All melting points are uncorrected IR spectra were obtained on a Pye Unicam SP 1000 Spectrophotometer using KBr discs. ^{1}H-nmr were recorded on a Varian EM 390-90 MHz, using TMS as internal reference. The chemical shifts were expressed as δ ppm. Analytical data were obtained from the Microanalytical Data Unit at Cairo University.

1,3-Dihydro-4,6-dimethyl-2-thioxopyridine-3-carbonitrile **IV**. A suspension of acetylacetone [1.0 g, 0.01 mole] in ethanol (20 ml) and catalytic amount of $(Et)_3N$ was treated with cyanothioacetamide [1.0 g, 0.01 mole]. The reaction mixture was heated under reflux for 3 hours, then left to cool. The resulting solution was poured over ice-water and acidified with a few drops of hydrochloric acid. The solid product, so formed, was collected by filtration and crystallized from dioxane to give 1.5 g (91%), of **IV** m.p. 235°C. The ^{1}H-nmr spectrum (DMSO) of **IV** shows signals of 2.35 (s, 3H, CH_3), 3.4 (s, 3H, CH_3), 6.7 (s, 1H, CH), 13.8 (broad, 1H, NH).—IR (KBr): 3430–3370 (NH), 2919 (CH_3), 2975 (CH_3), 2220 (CN), 1200–1190 cm^{-1} (C=S). Mass, m/z = 164 (M^+). Anal. Found (calcd.): C, 58.45 (58.53); H 4.8 (4.87); N, 17.00 (17.07); S, 19.45 (19.51).

Ethyl-5-Cyano-1,6-dihydro-4-methyl-1-phenyl-6-oxopyridazine-3-carboxylate (**I**). A mixture of equimolar amounts of phenylazoethyl acetoacetate (0.1 mole) and ethyl cyanoacetate [11.3 g, 0.1 mole] was heated in an oil bath at 160°C for 30 minutes. The resulting product was then triturated with ethanol, and the solid product, so formed, was collected by filtration and crystallized from ethanol to give 22.7 g (80%), of **I**, m.p. 152°C.—IR (KBr): 3000–2920 (CH_3, CH_2), 2220 (CN), 1725–1650 cm^{-1} (4 C=O). Mass. m/z = 284 (M^+). Anal. Found (calcd.): C, 63.50 (63.60); H, 4.56 (4.59); N, 14.80 (14.84).

Ethyl Dimethyl 5-amino-4-oxo-3-phenyl phthalazine-1,6,7-tricarboxylate (**II**). A solution of **I** [2.9 g, 0.01 mole], in pyridine (20 ml) was treated with dimethyl acetylenedicarboxylate (1.4 g, 0.01 mole). The reaction mixture was heated under reflux for 3 hours, then left to cool and the resulting solution was poured over ice-water. The solid product, so formed, was collected by filtration and crystallized from ethanol-DMF to give 2.5 g (60%), of **II**, m.p. 200°C.—IR (KBr): 3420, 3310 (NH_2); 3100 (CH aromatic), 2970 (CH_3), 1715 and 1670–1660 (4 C=O groups), 1640 (C=N), 1630 cm^{-1} (C=C). Mass: m/z = 426 (M^+). Anal. Found (calcd.): C, 59.11 (59.29); H, 4.36 (4.47); N, 9.79 (9.88).

Ethyl 5-Amino-3,7-diphenyl-4,6,8-trioxopyrrolo[3,4-g]phthalazine-1-carboxylate (**III**). A mixture of **I** [2.8 g, 0.01 mole], and N-phenylmaleimide 1.7 g, (0.01 mole) undergoes fusion reaction in an oil bath for about 30 minutes. Then the solid product, so formed, was collected by filtration and crystallized from ethanol to give 3.4 g (77%), of **III**, m.p. 100°C.—IR (KBr): 3429–3322 (NH_2); 3040 (CH aromatic), 2990 and 2928–2207 (CH_3, CH_2), 1726, 1653 and 1615 (4 C=O groups), 1605 cm^{-1} (C=N). Mass: m/z = 457 (M^+). Anal. Found (calcd.): C, 65.80 (66.07); H, 3.81 (3.96); N, 12.23 (12.33).

1,2-Dihydro-4-methyl-6-styryl-2-thioxopyridine-3-carbonitrile **VI**. Solution of **IV** [1.0 g, 0.01 mole] in pyridine (20 ml) was treated with benzylidene-malononitrile [1.5 g, 0.01 mole] (a) p-methoxybenzylidenemalononitrile [1.8 g, 0.01 mole] (b), or *p*-chlorobenzylidenemalononitrile [1.88 g, 0.01 mole] (c).

The reaction mixture was heated under reflux for 3 hours, then left to cool and the resulting solution was poured over ice-water. The solid product, so formed, was collected by filtration to give **VI** (cf. Table I).

1,2-Dihydro-4,6-distyryl-2-thioxopyridine-3-carbonitrile **VIII**. A solution of **VI** in pyridine (20 ml) was treated with benzylidene malononitrile [1.5 g, 0.01 mole]. The reaction mixture was heated under reflux for 3 hours, then left to cool and the resulting solution was poured over ice-water. The solid product, so formed, was collected by filtration and crystallized from ethanol to give 2.5 g (73.5%), of **VIII**, m.p. 170°C.—IR(KBr): 1620, 1570 (2 C=C), 1660 (C=N), 2220 (CN), 3050 (CH aromatic), 1220–1190 cm^{-1} (C=S). Mass. m/z = 339 (M − 1). Anal. Found (calcd.): C, 77.46 (77.64); H, 4.61 (4.70); N, 8.12 (8.23); S, 9.36 (9.41).

8-Amino-1,2-dihydro-3-styryl-1-thioxoisoquinoline-7-carbonitrile **XIa–c**. A solution of **VIa–c** in pyridine (20 ml) was treated with acrylonitrile [0.5 g, 0.01 mole]. The reaction mixture was heated under reflux for 5 hours, then left to cool and the resulting solution was poured over ice-water. The solid product, so formed, was collected by filtration to give **XIa–c** (cf. Table II).

4-Amino-1,3,5,6-tetrahydro-7-methyl-2-phenyl-5-thioxopyrrolo[3,4-g]thioxo-isoquinoline-1,3-dione **XIII**. A mixture of **IV** [1.6 g, 0.01 mole] and N-phenyl maleimide [1.7 g, 0.01 mole] undergoes fusion reaction in an oil bath for about 30 minutes. Then the solid product, so formed, was collected by filtration and crystallized from ethanol-dioxane to give 1.39 (79%); of **XIII**, m.p. 270°C.—IR (KBr): 3472–3440 (NH_2, NH), 3050 (CH aromatic), 2990 (CH_3), 1720–1690 (2C=O); 1220 cm^{-1} (C=S). Mass. m/z = 337 (M^+). Anal. Found (calcd.): C, 64.43 (64.47); H, 3.80 (3.88); N, 12.39 (12.53); S, 9.45 (9.55).

3-Methyl-1,2,5,6,7,8-hexahydro-8-imino-6,6,7,7-tetracyano-1-thioxoisoquinoline **XIV**. A solution of **IV** [1.6 g, 0.01 mole] in pyridine (20 ml) was treated with tetracyanoethylene [1.2 g, 0.01 mole]. The reaction mixture was heated under reflux for 5 hours, then left to cool, and the resulting solution was poured over ice-water. The solid product, so formed, was collected by filtration and crystallized from acetic acid to give 1.5 g (51%), of **XIV**, m.p. >300°C.—IR (KBr): 3390 (NH), 2990 (CH_3), 2250–2270 (4CN), 1650 (C=N), 1230 cm^{-1} (C=S). Mass: m/z = 294 (M^+). Anal. Found (calcd.): C, 57.37 (57.53); H, 2.70 (2.73); N, 28.68 (28.76); S, 10.92 (10.95).

2-(3-Cyano-4,6-dimethyl-pyridine-2-ylthio)maleic acid-1-methyl ester **XV**. A solution of **IV** [1.6 g, 0.01 mole] in pyridine (20 ml) was treated with dimethyl acetylenedicarboxylate [1.4 g, 0.01 mole]. The reaction mixture was heated under reflux for 3 hours, then left to cool and the resulting solution was poured over ice-water. The solid product, so formed was collected by filtration and crystallized from ethanol-DMF to give 1.5 g (51%), of **XV**, m.p. >300°C.—IR (KBr): 3470–3440 (NH_2-NH), 2970 (CH_3), 1700–1690 (2C=O), 1200 cm^{-1} (C=S). Mass: m/z = 291 (M − 1). Anal. Found (calcd.): C, 53.35 (53.42); H, 4.05 (4.10); N, 9.55 (9.58); S, 10.92 (10.95).

2-Phenacyl mercapto-4,6-dimethyl-pyridine-3-carbonitrile (**XVII**). A solution of **IV** [1.6 g, 0.01 mole] in pyridine (20 ml) was treated with phenacyl bromide [1.9 g, 0.01 mole]. The reaction mixture was heated under reflux for 3 hours, then left to cool, the resulting solution was poured over ice-water. The solid product, so formed, was collected by filtration and crystallized from ethanol-dioxane to give 2.2 g (80%), of **XVII**, m.p. 130°C.—IR (KBr): 3063 (CH aromatic), 2990, 2920 ($2CH_3$), 2213 (CN), 1693 (C=O), 1650 cm^{-1} (C=N). Mass: m/z = 281 (M − 1). Anal. Found (calcd.): C, 68.00 (68.08), H, 4.75 (4.96); N, 9.78 (9.92); S, 11.25 (11.34).

3-Amino-4,6-dimethyl-2-benzoylthieno[2,3-b]pyridine **XVIII**. A solution of **IV** [1.6 g, 0.01 mole] in pyridine (20 ml) was treated with phenacyl bromide [1.9 g, 0.01 mole]. The reaction mixture was heated under reflux 7 hours, then left to cool and the resulting solution was poured over ice-water. The solid product, so formed, was collected by filtration and crystallized from ethanol-dioxane to give 2.0 g (71%), of **XVIII**, m.p. 189°C.—IR (KBr): 3063 (CH aromatic), 3508–3330 (NH_2), 2920 ($2CH_3$), 1593 cm^{-1} (C=O). Mass: m/z = 282 (M^+). Anal. Found (calcd.): C, 68.00 (68.08); H, 4.75 (4.96); N, 9.78 (9.92); S, 11.15 (11.34).

Method (B). A solution of **XVII** [2.8 g, 0.01 mole] in (20 ml) sodium ethoxide was heated under reflux for 2 hours, then left to cool, and the resulting solution was poured over ice-water. The solid product, so formed, was collected by filtration and crystallized from thanol-dioxane to give 2.1 g (75%), of **XVIII**, m.p. 189°C.—IR (KBr): 3050 (CH aromatic), 3506–3330 (NH_2), 2990, 2920 ($2CH_3$), 1591 cm^{-1} (C=O). Mass: m/z = 282 (M^+). Anal. Found (calcd.): C, 68.00 (68.08); H, 4.75 (4.96); N, 9.78 (9.92); S, 11.15 (11.34).

2-Amino-7,9-dimethyl-4-phenylpyrido[2,3:2',3']thieno[5,4-b]pyridine-3-carbonitrile **XIX**. A solution of **XVII** [2.8 g, 0.01 mole] in pyridine (20 ml) was treated with malononitrile [0.66 g, 0.01 mole]. The reaction mixture was heated under reflux for 3 hours, then left to cool, the resulting solution was poured

over ice-water. The solid product so formed, was collected by filtration and crystallized from ethanol dioxane to give 2.1 g (74%), of **XIX**, m.p. 272°C.—IR (KBr): 3520–3400 (NH_2), 3060 (CH aromatic), 2990, 2920 ($2CH_3$), 2220 (CN), 1620 cm^{-1} (C=N). Mass: m/z = 331 (M + 1). Anal. Found (calcd.): C, 68.96 (69.09); H, 4.15 (4.24); N, 16.88 (16.96); S, 9.58 (9.69).

4,6-Dimethyl-2-phenacylhydrazonylmercaptopyridine-3-carbonitrile **XX**. A solution of **XVII** [2.8 g, 0.01 mole] in ethanol (20 ml) and a catalytic amount of $(Et)_3N$ was treated with hydrazine hydrate [0.5 ml, 0.01 mole]. The reaction mixture was heated under reflux for 3 hours, then left to cool. The solid product, so formed, was collected by filtration and crystallized from ethanol to give 2.0 g (70%), of **XX**, m.p. 168°C.—IR (KBr): 3510–3310 (NH_2), 2990, 2920 ($2CH_3$), 2220 (CN), 1600 cm^{-1} (C=N). Mass: m/z = 296 (M^+). Anal. Found (calcd.): C, 64.68 (64.86); H, 5.30 (5.40); N, 18.82 (18.91); S, 10.69 (10.81).

3-Amino-4,6-dimethyl-2-carbophenylhydrazonylthieno[2,3-b]pyridine **XXI**. A solution of **XVIII** [2.8 g, 0.01 mole] in ethanol (20 ml) and catalytic amount of Et_3N was treated with hydrazine hydrate [0.5 ml, 0.01 mole]. The reaction mixture was heated under reflux 3 hrs, then left to cool. The solid product, so formed, was collected by filtration and crystallized from ethanol to give 2.1 g (71%), of **XXI**, m.p. 198°C.—IR (KBr): 3501–3300 ($2NH_2$), 2990, 2920 cm^{-1} ($2CH_3$). Mass: m/z = 296 (M^+). Anal. Found (calcd.): C, 64.81 (64.86); H, 5.39 (5.40); N, 18.83 (18.91); S, 10.78 (10.81).

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