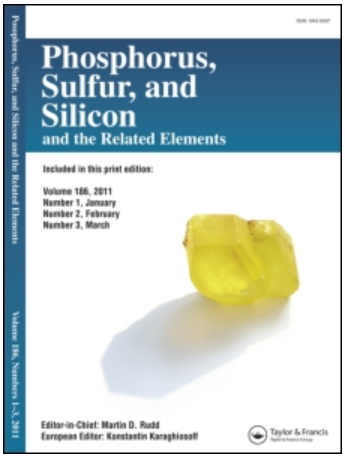

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SYNTHESIS AND SOME REACTIONS OF ARYLPYRIDYLSULFIDE DERIVATIVES

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SYNTHESIS AND SOME REACTIONS OF ARYLPYRIDYLSULFIDE DERIVATIVES

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The title compound (**I**) was prepared from the reaction of 2-chloro-3-cyano-4,6-dimethylpyridine and 4-bromonitrobenzene in aqueous sodium sulfide solution. Condensation of **I** with aromatic aldehydes, 2-methyl benzoxazin-4-one, azalactone and succinic anhydride afforded the expected products (**IV, VI, VIII** and **XV**). Coupling of diazotized **I** with active methylene compounds gave the corresponding hydrazones **Xa,b**. Cyclization of hydrazone **Xa** with $AlCl_3$ gave the cinnoline derivative **XII**, which condensed with phenylhydrazine to give the pyrazolocinnoline derivative **XIII**. Oxidation of some of the prepared sulfides with H_2O_2 in AcOH afforded the corresponding sulfones.

Key words: Synthesis; arylpyridylsulfides; quinazolin-4-one; imidazol-5-one; 1H-cinnolin-4-ones; succinimide.

INTRODUCTION

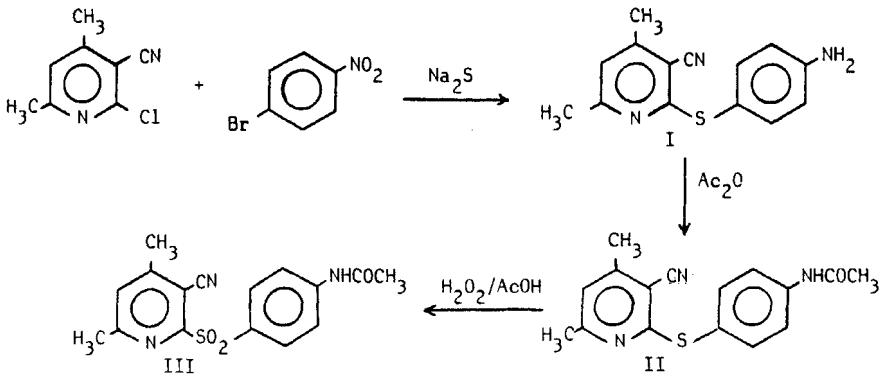
It is of interest to note that pyridine thiol derivatives incorporating aminophenyl moiety possess antithyroid activity[1] and also diarylsulfides containing pyridine nucleus showed marked antifungal activity.[2] On the other hand, dipyridylsulfides are useful as bactericides, fungicides and herbicides.[3] Within this respect, the present work aimed to synthesize some unreported arylpyridylsulfides[4] substituted by other heterocycles for biological interest.

The starting compound 2-(4′-aminophenylthio)-3-cyano-4,6-dimethylpyridine (**I**) was prepared by the reaction of *p*-bromo-nitrobenzene with 2-chloro-3-cyano-4,6-dimethylpyridine in aqueous sodium sulfide solution.

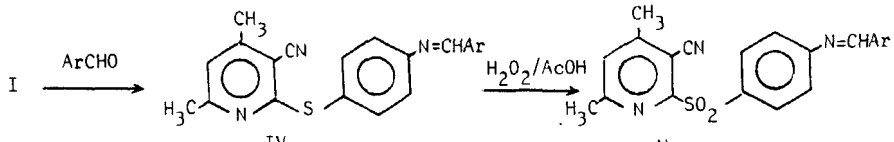
The chemical structure of **I** was confirmed by elemental analysis and spectral data. The IR spectrum showed absorption bands at 3430, 3340 cm^{-1} (NH_2) and at 2220 cm^{-1} (C≡N). The ^1H NMR spectrum in $CDCl_3$ showed the following signals: at δ 2.30 (s, 3H, CH_3), δ 2.40 (s, 3H, CH_3), δ 3.75 (s, 2H, NH_2), δ 6.70 (s, 1H, CH-pyridine), δ 6.55–6.65 (d, 2H, CH-Ar) and at δ 7.15–7.30 (d, 2H, CH-Ar).

Acetylation of **I** with acetic anhydride in benzene afforded the corresponding acetylamino derivative **II** which was oxidized with hydrogen peroxide in glacial acetic at room temperature to give the corresponding 2-(4′-acetylaminophenylsulphono)-3-cyano-4,6-dimethylpyridine (**III**).

The chemical structure of **II** and **III** was established by elemental analyses and IR spectra. The IR spectrum of **II** showed absorption bands at 3340 cm^{-1} (NH), 2230 cm^{-1} (C≡N) and 1720 cm^{-1} (C=O). The IR spectrum of **III** showed absorption bands at 3320 cm^{-1} (NH), 2230 cm^{-1} (C≡N) and at 1340, 1175 cm^{-1} (SO_2).



Condensation of **I** with aromatic aldehydes in ethanol in the presence of piperidine as a basic catalyst yielded a series of 2-(4′-arylideneaminophenylthio)-3-cyano-4,6-dimethylpyridines (**IVa–d**). Oxidation of **IVd** with hydrogen peroxide in acetic acid at room temperature gave the corresponding sulphone **V**.



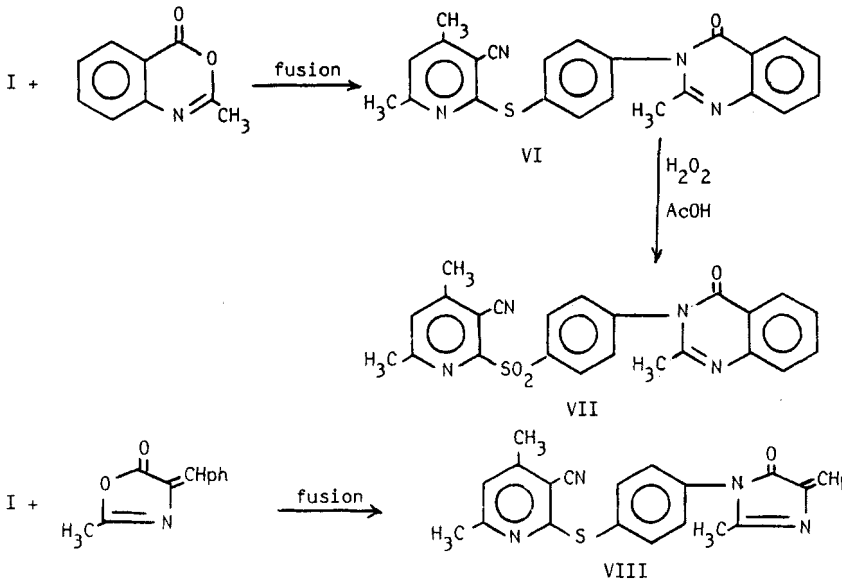
a, Ar = C_6H_5
b, Ar = $C_6H_4NO_2$(p)
c, Ar = $C_6H_4NMe_2$(p)
d, Ar = C_6H_4OH(o)

The chemical structure of **IVa–d** and **V** was confirmed by elemental analyses and spectral data. The IR spectra of compounds **IVa–d** showed an absorption band at 2200 cm^{-1} (C≡N) and the disappearance of the characteristic band due to NH_2 group, compound **IVd** showed additional absorption band at 3100 cm^{-1} due to the phenolic OH group. The ^1H NMR spectrum of **IVa** in $CDCl_3$ showed the following signals: at δ 2.30 (s, 3H, CH_3), δ 2.40 (s, 3H, CH_3), δ 6.70 (s, 1H, CH-pyridine), δ 7.05–7.80 (m, 9H, CH-Ar) and at δ 8.35 (s, 1H, CH=N). The ^1H NMR spectra of **IVc** in $CDCl_3$ showed the following signals: at δ 2.35 (s, 3H, CH_3), δ 2.45 (s, 3H, CH_3), δ 3.05 (s, 6H, $N(CH_3)_2$), δ 6.80 (s, 1H, CH-pyridine), δ 6.60–7.70 (m, 8H, CH-Ar) and at δ 8.20 (s, 1H, CH=N). The IR spectrum of **V** showed absorption bands at 3100 cm^{-1} (OH), 2230 cm^{-1} (C≡N) and at 1340, 1165 cm^{-1} (SO_2).

It was reported that 2,4-diamino-6-[(heterocyclic)thio, sulfinyl, and sulfonyl]quinazolines exhibit suppressive antimalarial activity against drug-sensitive lines of Plasmodium berghei in mice.[5] Also, 4-benzylidene-4,5-dihydro-5-oxo-3-methyl-1H-imidazole derivatives were evaluated for their anti-inflammatory activity.[6]

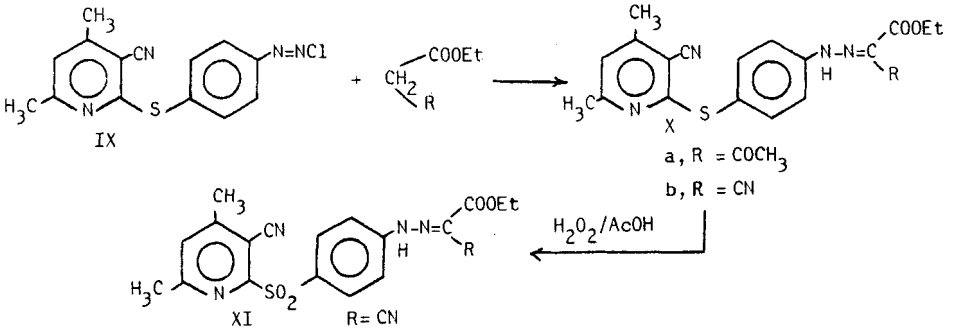
Fusion of **I** with 2-methyl benzoxazin-4-one at 170°C afforded the corresponding 2-methyl-3-[4′-(3″-cyano-4″-,6″-dimethylpyrid-2″-yl)thiophenyl]quinazol-4-one **(VI)**.

Oxidation of **VI** with H_2O_2 in acetic acid afforded the corresponding sulfone (**VII**). Similarly, fusion of **I** with 4-benzylidene-2-methyl oxazol-5-one at 140° yielded the corresponding 2-[4′-(4″-benzylidene-2″-methyl-5″-oxo-imidazol-1″-yl) phenylthio]-3-cyano-4,6-dimethylpyridine (**VIII**).



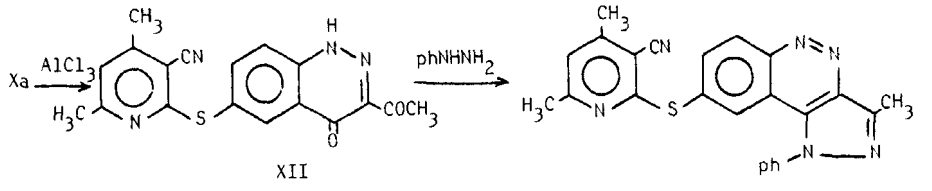
The chemical structure of compounds **VI–VIII** was confirmed on the basis of their elemental analyses and spectral data. The IR of **VI** showed absorption bands at 2220 cm^{-1} (C≡N) and at 1690 cm^{-1} (C=O). The ^1H NMR of **VI** in $CDCl_3$ showed the following signals: at δ 2.55 (s, 6H, 2 CH_3), at δ 2.60 (s, 3H, CH_3), δ 7.20 (s, 1H, CH-pyridine) and at δ 7.30–8.20 (m, 8H, CH-Ar). The IR spectrum of **VII** showed absorption bands at 2240 cm^{-1} (C≡N), 1690 cm^{-1} (C=O) and at 1320, 1150 cm^{-1} (SO_2). The IR spectrum of **VIII** showed absorption bands at 2210 cm^{-1} (C≡N) and at 1710 cm^{-1} (C=O).

Coupling of diazotized **I** (**IX**) with active methylene compounds namely ethyl acetoacetate and ethyl cyanoacetate in aqueous alcoholic solution containing sodium acetate result in the formation of the corresponding hydrazones (**Xa, b**). Oxidation of Xb with H_2O_2/AcOH at room temperature afforded the corresponding sulfone (**XI**).



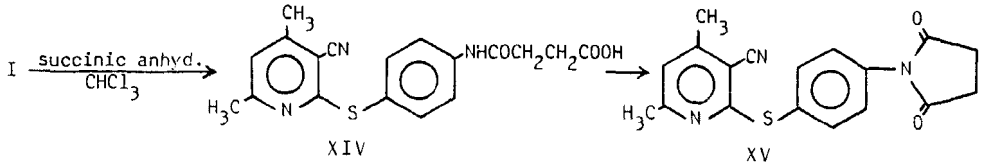
The chemical structure of compounds **Xa,b** and **XI** was confirmed by elemental and spectral analyses. The IR spectrum of **Xa** showed absorption bands at 3020-2840 cm^{-1} (NH), 2220 cm^{-1} (C≡N) and at 1710 cm^{-1} (C=O). The ^1H NMR spectrum of **Xa** in $CDCl_3$ showed the following signals: at δ 1.35–1.50 (t, 3H, CH_3 of ester), δ 2.40 (s, 3H, CH_3), δ 2.45 (s, 3H, CH_3), δ 2.50 (s, 3H, $COCH_3$), δ 4.20–4.45 (q, 2H, CH_2 of ester), δ 6.75 (s, 1H, CH-pyridine), δ 7.25–7.55 (m, 4H, CH-Ar) and at δ 12.65 (s, 1H, NH). The IR spectrum of **Xb** showed absorption bands at 2220 cm^{-1} (C≡N) and at 1725, 1670 cm^{-1} (C=O), while the IR spectrum of **XI** showed absorption bands at 2220 cm^{-1} (C≡N), 1740, 1675 cm^{-1} (C=O) and at 1330, 1150 cm^{-1} (SO_2). The ^1H NMR spectrum of **XI** in CF_3COOH showed signals at δ 1.35–1.50 (t, 3H, CH_3, ester), δ 2.65 (s, 6H, $2CH_3$ of pyridine ring), δ 4.25–4.5 (q, 2H, CH_2 ester), δ 7.40 (s, 1H, CH-pyridine) and at δ 7.45–8.2 (m, 4H, CH-Ar).

The hydrazone **Xa** was exploited to synthesize a fused 1,2-diazine ring by its intramolecular cyclization with anhydrous aluminum chloride in chlorobenzene[7] to give 3-acetyl-6-[(3′-cyano-4′,6′-dimethylpyrid-2′-yl)thio]-1H-cinnolin-4-one (**XII**). Interaction of **XII** with phenylhydrazine led to the formation of 3-methyl-1-phenyl-8-[(3′-cyano-4′,6′-dimethylpyrid-2′-yl) thio]-1H-pyrazolo[4,3-c]cinnoline (**XIII**).



The chemical structure of **XII** and **XIII** was elucidated from their elemental and spectral analyses. The IR spectrum of **XII** showed absorption bands at 3120 cm^{-1} (NH), 2220 cm^{-1} (C≡N) and at 1685 cm^{-1} (C=O). The ^1H NMR spectrum in $CDCl_3$ showed the following signals: at δ 2.40 (s, 3H, CH_3), δ 2.50 (s, 3H, CH_3), δ 2.60 (s, 3H, $COCH_3$), δ 6.85 (s, 1H, CH-pyridine), δ 7.35–7.65 (m, 3H, CH-Ar) and at δ 14.10 (s, 1H, NH). The IR spectrum of **XIII** showed absorption bands at 2230 cm^{-1} (C≡N) and at 1660 cm^{-1} (C=N).

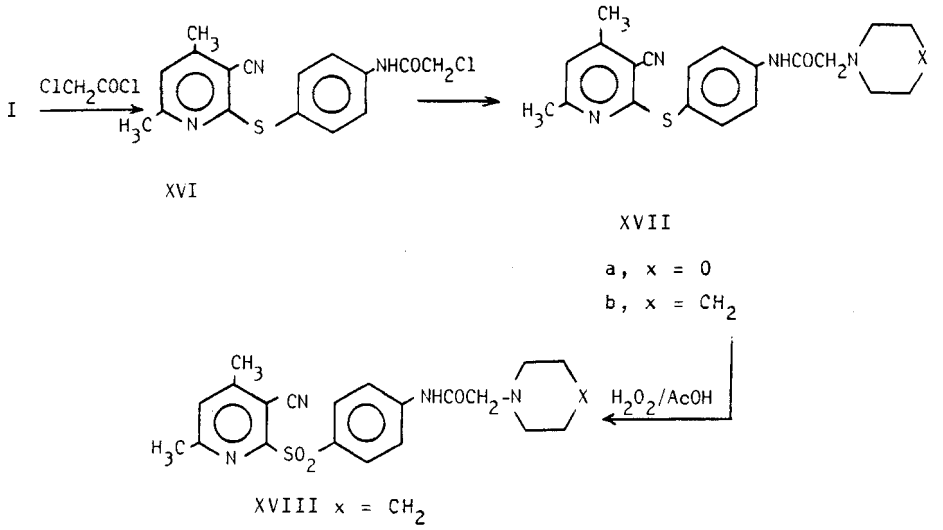
Reaction of **I** with succinic anhydride in boiling chloroform gave 2-(4′-succinamidophenylthio)-3-cyano-4,6-dimethylpyridine (**XIV**) which was subsequently cyclized with sodium acetate in acetic acid to give 2-[4′-(N-succinimidylphenyl)-thio]-3-cyano-4,6-dimethylpyridine (**XV**).



The chemical structure of **XIV** and **XV** was confirmed by elemental analyses and spectral data. The IR spectrum of **XIV** showed absorption bands at 3380-2800 cm^{-1}

(NH and OH-carboxylic acid), 2220 cm^{-1} (C≡N), 1720 cm^{-1} (C=O acid) and at 1670 (C=O amide). The ^1H NMR spectrum of **XV** in $CDCl_3$ showed the following signals: at δ 2.60 (s, 6H, 2 CH_3), δ 2.95 (s, 4H, CO CH_2CH_2CO), δ 7.10 (s, 1H, CH-pyridine) and at δ 7.30–7.60 (m, 4H, CH-Ar).

Compounds containing the aminoacetylamide grouping —NH $CO(CH_2)_nN$< have been shown to have very interesting medical properties especially as local anesthetics.[8,9] So, the starting material **I** was chloroacetylated with chloroacetyl chloride in refluxing toluene to give the chloroacetylamino derivative (**XVI**). Reaction of **XVI** with morpholine or piperidine furnished the corresponding 2-[4'(N-morpholino- or piperidino acetyl amino)phenylthio]-3-cyano-4,6-dimethyl-pyridine (**XVIIa,b**). Oxidation of **XVIIb** with H_2O_2/AcOH afforded the corresponding sulfone (**XVIII**).



The chemical structure of compounds **XVI–XVII** was elucidated from their elemental and spectral analyses. The IR spectrum of **XVIIb** showed absorption bands at 3290 cm^{-1} (NH), 2940 cm^{-1} (CH-aliph.), 2225 cm^{-1} (C≡N) and at 1695 cm^{-1} (C=O). The ^1H NMR of **XVIIb** in $CDCl_3$ showed the following signals: at δ 9.40 (s, 1H, NH), δ 7.65-7.40 (m, 4H, CH-Ar), δ 6.80 (s, 1H, CH-pyridine ring), δ 3.10 (s, 2H, $COCH_2$), δ 2.65-2.50 (m, 4H, 2 CH_2-piperidine ring), δ 2.45 and δ 2.35 (2s, 6H, 2 CH_3) and at δ 1.90-1.40 (m, 6H, 3 CH_2-piperidine ring). The IR spectrum of **XVIII** showed absorption bands at 3250 cm^{-1} (NH), 2210 cm^{-1} (C=N), 1660 cm^{-1} (C=O) and at 1335, 1160 cm^{-1} (SO_2).

EXPERIMENTAL

All melting points are uncorrected and measured on Fisher-Johns melting point apparatus. Elemental analyses were performed on a Perkin-Elmer 240 elemental analyser. IR spectra were recorded on a Pye-Unicam SP 3-100 spectrophotometer using KBr wafer technique. ^1H NMR spectra were recorded on a Varian EM-390 90 MHz spectrometer in suitable deuterated solvent using TMS as internal standard.

2-(4'-Aminophenylthio)-3-cyano-4,6-dimethylpyridine (I): A mixture of 4-bromonitrobenzene (16.08 g, 0.08 mol) and sodium sulfide trihydrate (52.8 g, 0.4 mol) in distilled water (200 ml) was refluxed for

6 hrs. 2-Chloro-3-cyano-4,6-dimethylpyridine (13.32 g, 0.08 mol) was added and reflux was continued for further 2 hrs. The precipitated solid was filtered off, dried and recrystallised from ethanol into white crystals m.p. 147-9°C, yield 13.46 g (66%).

Anal. Calcd. for $C_{14}H_{13}N_3S$: C, 65.86; H, 5.13; N, 16.46; S, 12.56
Found: C, 65.80; H, 5.10; N, 16.55; S, 12.60.

2-(4'-Acetylaminophenylthio)-3-cyano-4,6-dimethylpyridine(II): A mixture of **I** (0.01 mol) and acetic anhydride (0.01 mol) in benzene (30 ml) was refluxed for 2 hr. The solid obtained on concentration and cooling was crystallized from ethanol into white crystals m.p. 194-6°C, yield 85%.

Anal. Calcd. for $C_{16}H_{15}N_3OS$: C, 64.62; H, 5.08; N, 14.13; S, 10.78.
Found: C, 64.50; H, 5.00; N, 14.26; S, 10.80

2-(4'-Arylideneaminophenylthio)-3-cyano-4,6-dimethylpyridines (IVa–d): A mixture of **I** (0.01 mol) and appropriate aromatic aldehyde (0.015 mol) in ethanol (30 ml) containing a few drops of piperidine was refluxed for 2 hrs. The precipitated solid was filtered off, dried and recrystallised from ethanol/benzene mixture.

Results are summarized in Table I.

2-Methyl-3-[4'-(3"-cyano-4",6"-dimethylpyrid-2"-yl)thiophenyl]-quinazol-4-one (VI): Compound **I** (0.02 mol) and 2-methylbenzoxazin-4-one (0.02 mol) were heated in an oil bath at 170-2°C for one hour. The solidified product was refluxed with ethanol (50 ml) and cooled. The product was recrystallised from benzene into white crystals m.p. 244-6°C, yield 4.6 g (58%).

Anal. Calcd. for $C_{23}H_{18}N_4OS$: C, 69.33; H, 4.55; N, 14.06; S, 8.05.
Found: C, 69.30; H, 4.54; N, 14.00; S, 8.12.

TABLE I

Physical data of some compounds prepared

Comp. No.	M.P. °C	Solvent of cryst.	Yield %	Molecular formula	Elemental analysis Calcd./Found %			
					C	H	N	S
IVa	161-3	B-E	82	$C_{21}H_{17}N_3S$	73.44 73.49	4.99 5.10	12.23 12.35	9.33 9.44
IVb	195-7	B-E	72	$C_{21}H_{16}N_4O_2S$	64.93 65.11	4.15 4.22	14.42 14.50	8.25 8.35
IVc	201-3	B-E	68	$C_{23}H_{22}N_4S$	71.47 71.52	5.74 5.79	14.50 14.42	8.29 8.32
IVd	178-80	B-E	80	$C_{21}H_{17}N_3OS$	70.17 70.18	4.77 4.88	11.69 11.73	8.92 9.13
Xa	140-2	E or B-P	88	$C_{20}H_{20}N_4O_3S$	60.59 60.60	5.08 5.10	14.13 14.15	8.09 8.10
Xb	174-6	B	90	$C_{19}H_{17}N_5O_2S$	60.14 60.20	4.52 4.50	18.46 18.50	8.45 8.60
XVIIa	133-5	P	75	$C_{20}H_{22}N_4O_2S$	62.80 62.73	5.80 5.88	14.65 14.67	8.38 8.33
XVIIb	163-5	B	78	$C_{21}H_{24}N_4OS$	66.29 66.21	6.36 6.22	14.72 14.70	8.43 8.50
III	220-2	B-E	32	$C_{16}H_{15}N_3O_3S$	58.35 58.40	4.59 4.63	12.76 12.82	9.73 9.60
V	211-2	A	47	$C_{21}H_{17}N_3O_3S$	64.44 64.44	4.38 4.35	10.73 10.66	8.19 8.22
VII	309-11	B-E	42	$C_{23}H_{18}N_4O_3S$	64.17 64.23	4.21 4.25	13.01 13.12	7.45 7.50
XI	233-5	A	36	$C_{19}H_{17}N_5O_4S$	55.47 55.53	4.16 4.26	17.02 17.12	7.79 7.84
XVIII	207-9	E	28	$C_{21}H_{24}N_4O_3S$	61.15 61.23	5.86 5.88	13.58 13.66	7.77 7.75

A = acetic acid B = Benzene E = ethanol P = Pet.ether (60-80°C).

2-[4'-(4"-Benzylidene-2"-methyl-5"-oxo-imidazo-1"-yl)phenylthio]-3-cyano-4,6-dimethylpyridine (VIII): Compound **I** (5.1 g, 0.02 mol) and 4-benzlidene-2-methyloxazol-5-one (3.74 g, 0.02 mol) were heated in an oil bath at 140°C for one hour. The solid product was triturated with ethanol, filtered off, dried and recrystallized from benzene m.p. 232-4°C. yield 4 g (47%).

Anal. Calcd. for $C_{25}H_{20}N_4OS$: C, 70.73; H, 4.75; N, 13.20; S, 7.55.
Found: C, 70.60; H, 4.80; N, 13.20; S, 7.60.

Coupling of diazotized I (IX) with active methylene compounds. Formation of Xa,b: To a solution of **I** (2.55 g, 0.01 mol) in a mixture of conc. HCl (5 ml) and water (10 ml), a solution of sodium nitrite (1 g) in water (10 ml) was added dropwise with stirring at 5°C during 5 min. The resulting diazonium salt (**IX**) was added dropwise with stirring to a cold solution of ethyl acetoacetate or ethyl cyanoacetate (0.01 mol) in a mixture of ethanol (30 ml), water (20 ml) and sodium acetate (5 g). The precipitated solid was collected, washed with water, dried and recrystallised from the proper solvent. Results are summarized in Table I.

3-Acetyl-6-[(3'-cyano-4',6'-dimethylpyrid-2'-yl)thio]-1H-cinnolin-4-one (XII): A mixture of Xa (3.96 g, 0.01 mol) and anhydrous aluminum chloride (2.66 g, 0.02 mol) in chlorobenzene (50 ml) was refluxed for one hour. The complex formed was cooled, decomposed by conc. HCl (20 ml) and diluted with ice-water mixture. The solid formed was collected, washed with water and recrystallised from acetic acid into yellow crystals m.p. 226-8°C, yield 2.4 g (68%).

Anal. Calcd. for $C_{18}N_{14}N_4O_2S$: C, 61.70; H, 4.03; N, 15.99; S, 9.15.
Found: C, 61.77; H, 4.10; N, 16.10; S, 9.20.

3-Methyl-1-phenyl-8-[(3'-cyano-4',6'-dimethylpyrid-2'-yl)thio]-1H-pyrazolo[4,3-c]cinnoline (XIII): Compound **XII** (1.75 g, 0.005 mol) and phenylhydrazine (0.5 ml, 0.005 mol) were refluxed in glacial acetic acid for 5 hrs. The solid obtained was recrystallised from acetic acid into yellow crystals m.p. 218-20°C, yield 1.5 g (71%).

Anal. Calcd. for $C_{24}H_{18}N_6S$: C, 68.23; H, 4.29; N, 19.89; S, 7.59.
Found: C, 68.25; H, 4.35; N, 19.90; S, 7.60.

2-(4'-Succinamidophenylthio)-3-cyano-4,6-dimethylpyridine (XIV): A mixture of **I** (1.275 g, 0.005 mol) and succinic anhydride (0.5 g, 0.005 mol) in chloroform (30 ml) was refluxed for 30 min. The precipitated product was collected and recrystallised from ethanol into white crystals, m.p. 208-10°C, yield 1.7 g (96%).

Anal. Calcd. for $C_{18}H_{17}N_3O_3S$: C, 60.83; H, 4.79; N, 11.82; S, 9.02
Found: C, 60.90; H, 4.85; N, 11.70; S, 9.15.

2-[4'-(N-Succinimidylphenyl)thio]-3-cyano-4,6-dimethylpyridine (XV): Compound **XIV** (1 g) and sodium acetate (1 g) in acetic acid (20 ml) were heated under reflux for 2 hrs. On cooling and dilution with water, the precipitated solid was recrystallised from ethanol, m.p. 248-50°C, yield, 0.8 g (84%).

Anal. Calcd. for $C_{18}H_{15}N_3O_2S$: C, 64.08; H, 4.48; N, 12.45; S, 9.50.
Found: C, 64.20; H, 4.50; N, 12.55; S, 9.54.

Chloroacetylation of I·Formation of XVI: To a solution of I (2.55 g, 0.01 mol) in toluene (30 ml), chloroacetyl chloride (2 ml) was added dropwise and the mixture was refluxed for 30 min. On cooling, the precipitated solid was filtered off and recrystallised from benzene m.p. 168-70°C yield, 2.6 g (78%).

Anal. Calcd. for $C_{16}H_{14}N_3OSCl$: C, 57.92; H, 4.25; N, 12.66; S, 9.66; Cl, 10.68
Found: C, 57.88; H, 4.30; N, 12.63; S, 9.50; Cl, 10.65.

2-[4'-(N-morpholino- or piperidinoacetylamino)phenylthio]-3-cyano-4,6-dimethylpyridine (XVIIa,b): Chloroacetyl derivative (**XVI**) (0.33 g, 0.001 mol) and morpholine or piperidine (0.003 mol) were refluxed in benzene (20 ml) for 2 hr. The precipitated salt was filtered and the solution was concentrated whereby a solid precipitate was formed. The product was recrystallised from benzene.
Results are summarized in Table I.

Oxidation with H_2O_2/AcOH: To a solution of **II**, **IVd**, **VI**, **Xb** or **XVII** (0.3 g) in glacial acetic acid (20 – 30 ml) was added dropwise hydrogen peroxide (5 ml, 30%). The mixture was kept at room temperature for 5–7 days, whereby crystalline products were deposited, collected and recrystallized from dilute acetic acid. Results are summarized in Table I.

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