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Synthesis and Biological Activities of Some New Pyrimidine Derivatives

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Synthesis of 4-chloro-5-cyano-2-methyl-6-phenylpyrimidine (Ib) and its reactions with acetamidine hydrochloride, guanidine hydrochloride, cyanoacetamide, benzilmonohydrazone, sodium azide, semicarbazide hydrochloride, acidhydrazides, active methylene compounds, aromatic amines and thiourea have been investigated. Also, the reactions of 5-cyano-2-methyl-6-phenyl-4 (3H)-pyrimidinethione (IXf) with ethyl iodide, ethyl chloroacetate, phenacyl bromide, acrylonitrile and chloroheterocycle systems were reported.

INTRODUCTION

Earlier we have been reporting the synthesis and reactions of some new pyridazine derivatives[1–5]. In view of the significant biological activities of the compounds having pyrimidine nucleus[6,7], the present investigation is concerned with the use of 4-chloro-5-cyano-2-methyl-6-phenylpyrimidine (Ib) and 5-cyano-2-methyl-6-phenyl-4 (3H)-pyrimidinethione (IXf) for the synthesis of some fused pyrimidine heterocycles and pyrimidine derivatives of a new type and it therefore appears likely that these compounds will exhibit interesting biological properties.

RESULTS AND DISCUSSION

A convenient route developed for the synthesis of 4-chloro-5-cyano-2-methyl-6-phenylpyrimidine (Ib) is by refluxing 5-cyano-2-methyl-6-phenyl-4-(3H)-pyrimidinone (Ia) with $POCl_3$–PCl_5 mixture in the presence of N,N-dimethylaniline.

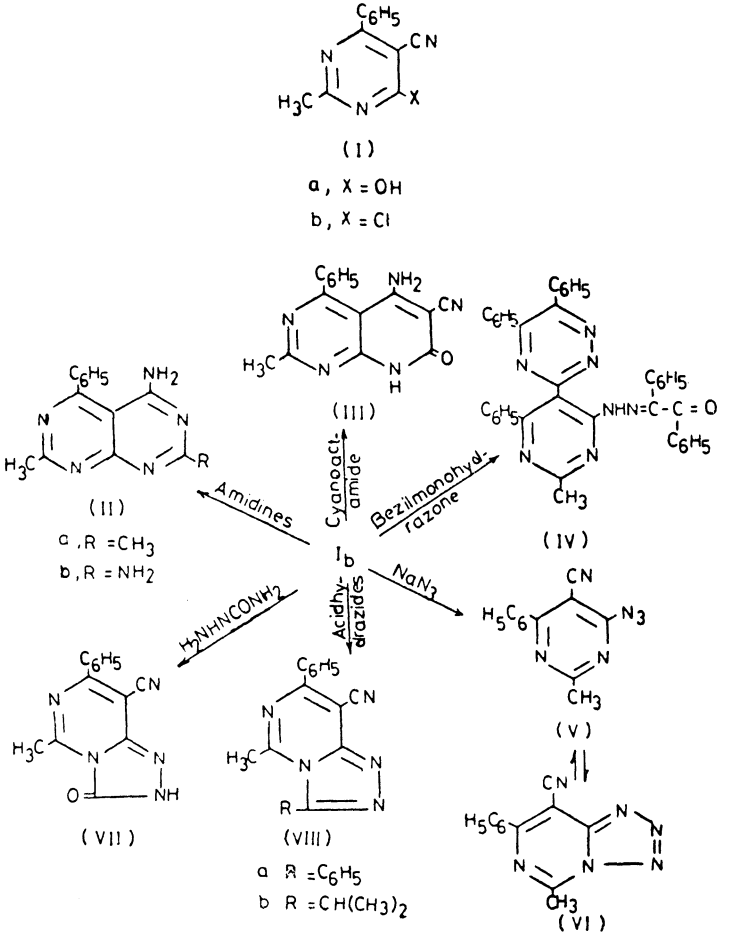
4-Chloro-5-cyano-2-methyl-6-phenylpyrimidine (Ib) with a vicinal chlorocyano group was envisioned as a potential starting material for the synthesis of some fused heterocycle systems. Thus, treatment of (Ib) with acetamidine hydrochloride or guanidine hydrochloride in sodium ethoxide yielded 4-amino-5-phenyl-2,7-dimethylpyrimido [4, 5-d] pyrimidine (IIa) and 2,4-diamino-5-phenyl-7-methylpyrimido [4, 5-d] pyrimidine (IIb) respectively, while reaction of (Ib) with cyanoacetamide in DMF gave 5-amino-6-cyano-2-methyl-4-phenylpyrido [2, 3-d] pyrimidine-7 (8H)-one (III).

Compound (Ib) when heated with benzilmonohydrazone in absolute ethanol ring closure took place to give 4-(α-benzoylbenzylidene-hydrazino)-5-[5′, 6′-diphenyl-1′,2′,4′-triazin-3′-yl]-2-methyl-6-phenyl-pyrimidine (IV). The IR spectrum of IV revealed the absence of the band which could be assigned to the cyano function.

Azidopyrimidine (V) was prepared by the reaction of chloropyrimidine (Ib) with sodium azide in DMF. Like similar heterocyclic azides[8] having the azido group attached to the cyclic carbon atom adjacent to an annular nitrogen, it may exist as true azide (V) or as tetrazolo [1, 5-c] pyrimidine (VI). Azido absorption band at 2160 cm^{-1} is absent in KBr disk, absorption bands at 1595 cm^{-1} (N=N) and 1170 cm^{-1} (tetrazolo) are present. This favours the proposed tetrazolo structure in the solid state.

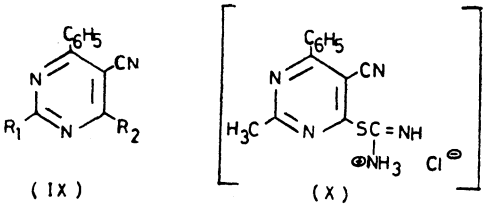
8-Cyano-5-methyl-7-phenyl-*s*-triazolo [4, 3-c] pyrimidine-3 (2H)-one (VII) was obtained by treatment of Ib with semicarbazide hydrochloride. Also, *s*-triazolo [4, 3-c] pyrimidine (VIIIa,b) were synthesized from Ib by the action of acidhydrazides (Scheme I).

SCHEME I



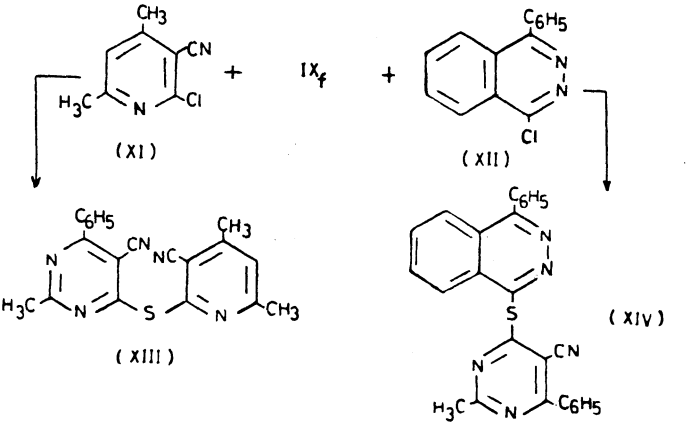
The chlorine atom at position 4 in compound (Ib) showed distinct activity towards nucleophilic reagents. Thus, nucleophilic substitution of the chlorine atom in (Ib) by reaction with active methylene compounds (*e.g.* ethyl cyanoacetate and malononitrile) or aromatic amines (namely, *p*-toluidine and p-anisidine) readily afforded 4-(α-cyanocarbethoxymethyl)-5-cyano-2-methyl-6-phenylpyrimidine (IXa), 4-(dicyanomethyl)-5-cyano-2-methyl-6-phenylpyrimidine (IXb), 4-(*p*-toluidino)-5-cyano-2-methyl-6-phenylpyrimidine (IXc) and 4-(*p*-anisidino)-5-cyano-2-methyl-6-phenylpyrimidine (IXd) respectively (Scheme II).

SCHEME II



(IX) (X)

a. $R_1 = CH_3$; $R_2 = CH(CN)COOC_2H_5$.
b, $R_1 = CH_3$; $R_2 = CH(CN)_2$.
c, $R_1 = CH_3$; $R_2 = NHC_6H_4CH_3\text{-}p$.
d, $R_1 = CH_3$; $R_2 = NHC_6H_4OCH_3\text{-}p$
e, $R_1 = (CH{=}CH)_2C_6H_5$; $R_2 = Cl$
f, $R_1 = CH_3$; $R_2 = SH$.
g, $R_1 = CH_3$; $R_2 = SC_2H_5$.
h, $R_1 = CH_3$, $R_2 = SCH_2COOC_2H_5$.
i, $R_1 = CH_3$, $R_2 = SCH_2COC_6H_5$.
j, $R_1 = CH_3$, $R_2 = SCH_2CH_2CN$.



(XI) IX$_f$ (XII) (XIII) (XIV)

On the other hand, condensation of (Ib) with cinnamaldehyde gave 4-phenyl-1-[4′-chloro-5′-cyano-6-phenylpyrimidin-2-yl] butadiene (IXe).

Thiourea, which appears to have a combination of considerable nucleophilic power and weak base strength[9], reacts readily with (Ib) to give 5-cyano-2-methyl-6-phenyl-4 (3H)-pyrimidinethione (IXf) through initially formed isothiuronium salt (X) as intermediate.

4 (3H)-Pyrimidinethione (IXf) is readily alkylated on the exocyclic sulphur atom when treated with ethyl iodide, ethyl chloroacetate and phenacyl bromide giving the corresponding *S*-alkylated derivatives (IXg–i) respectively.

In the reaction of (IXf) with acrylonitrile, cyanoethylation took place on the exocyclic sulphur yielding 4-(β-cyanoethylthio)-5-cyano-2-methyl-6-phenylpyrimidine (IXj).

Treatment of (IXf) with 2-chloro-4,6-dimethylpyridine[10] (XI) and 1-chloro-4-phenylphthalazine[11] (XII) afforded 3-cyano-2-[5′-cyano-2′-methyl-6′-phenylpyrimidin-4′-ylthio]-4,6-dimethylpyridine (XIII) and 4-phenyl-1-[5′-cyano-2′-methyl-6′-phenylpyrimidin-4′-ylthio] phthalazine (XIV) respectively (Scheme II).

Antibacterial and Antifungal Activities

The biological activities of some new synthesized compounds were tested against Gram positive bacteria (*Bacillus punilus* and *Sarcina lutea*), Gram negative bacteria (*Escherichia coli* and *Salmonela wild*), Acid fast bacterium (*Mycobacterium phlei*), an yeast (*Candida albicans*) and a filamentous fungus (*Aspergillus niger*).

TABLE 1

Compound	Antimicrobial Activity MIC μ gm/mL						
	G+ve[a]		G−ve[b]		Acid fast[c]	Fungi[d]	
	B.p.	S.l.	E.c.	S.w.	M.p.	C.a.	A.n.
IIa	> 100	> 100	> 100	> 100	> 100	> 100	> 100
III	100	> 100	> 100	> 100	50	> 100	> 100
VIIIa	> 100	> 100	> 100	50	> 100	> 100	> 100
IXc	> 100	> 100	> 100	> 100	> 100	> 100	> 100
IXd	> 100	> 100	> 100	> 100	> 100	> 100	> 100
IXe	> 100	> 100	> 100	50	> 100	> 100	> 100
IXj	> 100	> 100	> 100	> 100	> 100	100	> 100
XIV	> 100	> 100	> 100	50	> 100	100	> 100

[a] B.p. = *Bacillus punilus*, S.l. = *Sarcina lutea*,
[b] E.c. = *Escherichia coli*, S.w. = *Salmonela wild*,
[c] M.p. = *Mycobacterium phlei*,
[d] C.a. = *Candida albicans*, A.n. = *Aspergillus niger*.

According to filter paper disc method[12], small discs of filter paper of uniform thickness and size containing graded amount of the agent to be tested were dipped into the seeded plates contain the antimicrobial solutions to be assayed, left for diffusion and incubated at 37° for 24 hrs. for the bacterial growth and at 24° for 4 days for the fungal growth. The agent diffuses into the agar and prevents the growth of the microorganism in a clear zone around the disc.

The above Table 1 shows that compounds VIIIa, IXe and XIV have activities against S.w.; IXj and XIV have activities against C.a.; Compound III has activity against B.p. and M.p. None of these compounds have activity against a filamentous fungus.

EXPERIMENTAL

All melting points reported are uncorrected, the IR spectra (KBr) were recorded on Perkin-Elmer 598 spectrophotometer and H^1 nmr. spectra were determined on Perkin-Elmer R12A instrument.

Formation of IIa, b

To a solution of sodium ethoxide [prepared from 0.5g. (0.02 mole) of sodium and 50 mL of absolute ethanol] acetamidine hydrochloride or guanidine hydrochloride (0.01 mole) was added and refluxed for 1 hr. Compound Ib (0.01 mole) in absolute ethanol (20 mL) was added dropwise. After being well stirred the reaction mixture was refluxed for 6 hrs. The solid obtained upon dilution with water was filtered off and recrystallized from the proper solvent to give (IIa, b) as yellow crystals respectively.

Compound IIa. m.pt. 272–3°C (DMF), (yield 82%). (Found : C, 67.00; H, 5.00; N, 27.60; $C_{14}H_{13}N_5$ requires C, 66.93; H, 5.17; N. 27.88). IR : 3390 (NH_2) and 1620 cm^{-1} (C=N and C=C). H^1 nmr spectrum (DMSO-d_6) δ 2.7 (s, 3H, C_7–CH_3), δ 3.0 (s, 3H, C_2–CH_3), δ 3.5 (s, 2H, NH_2) and δ 7.6 ppm (m, 5H, aromatic protons).

Compound IIb. m.pt. 265–6°C (ethanol), (yield 75%), (Found : C, 62.00: H, 4.60; N, 33.20; $C_{13}H_{12}N_6$ requires C, 61.90; H, 4.76; N, 33.33). IR : 3420 (NH_2) and 1620 cm^{-1} (C=N and C=C).

5-Amino-6-Cyano-2-Methyl-4-Phenylpyrido [2,3-d] Pyrimidin-7 (8H)-One (III)

A mixture of (Ib) (0.01 mole), sodium carbonate (5 g.) and cyanoacetamide (0.01 mole) in DMF (30 mL) was refluxed for 6 hrs., poured onto cold water. The solid obtained was filtered off and recrystallized from DMF-water to give (III) as brown crystals, m.pt. > 280°C (yield 65%). (Found: C, 65.00; H, 4.10; N, 25.30 : $C_{15}H_{11}N_5O$ requires C, 64.98; H, 3.97; N, 25.27). IR:3200 (NH_2 and NH), 2220 (C=N) and 1720 cm^{-1} (C=O). H^1 nmr

(*DMSO-d_6*) δ 2.6 (s, 3H, C_2–CH_3), δ 3.8 (s, 2H, NH_2) and δ 7.7 ppm (m, 6H, aromatic protons and NH).

Formation of (IV)

A mixture of (Ib) (0.01 mole) and benzilmonohydrazone (0.01 mole) in absolute ethanol (30 mL) was refluxed for 2 hrs. The solid obtained was filtered off and recrytallized from DMF to give (IV) as yellow crystals, m.pt. 245–6°C (yield 85%). (Found : C, 77.70; H, 4.60; N, 15.60; $C_{40}H_{29}N_7O$ requires C, 77.40; H, 4.65; N, 15.75). IR: 3340 (NH) and 1640 cm^{-1} (C=O).

8-Cyano-5-Methyl-7-Phenyltetrazolo [1,5-c] Pyrimidine (VI)

A mixture of (Ib) (0.01 mole) in DMF (20 mL) and sodium azide (0.01 mole) in water (2 mL) was refluxed for 3 hrs. diluted with water and neutralized with dil HCl. The solid obtained was filtered off and recrystallized from acetic acid to give (VI) as yellow crystals, m.pt. 280–1°C (yield 86%). (Found : C, 54.70; H, 3.00; N, 42.30; $C_{12}H_8N_6$ requires C, 54.54; H, 3.03; N, 42.42).

Formation of (VII)

A mixture of (Ib) (0.01 mole) and semicarbazide hydrochloride (0.012 (mole) in absolute ethanol (30 mL) was treated with few drops of conc. HCl and refluxed for 18 hrs. The solid obtained was filtered off and recrystallized from ethanol to give (VII) as yellow crystals, m.pt. 235–6°C (yield 72%). (Found : C, 62.20: H, 3.60; N, 27.80; $C_{13}H_9N_5O$ requires C, 62.15; H, 3.58; N, 27.88). IR : 3320 (NH), 2220 (C≡N) and 1680 cm^{-1} (C=O).

8-Cyano-5-Methyl-3,7-Diphenyl-*s*-Triazolo [4,3-c] Pyrimidine (VIIIa)

A mixture of (Ib) (0.01 mole) and benzoic acidhydrazide (0.012 mole) in butanol (30 mL) was refluxed for 72 hrs. The solid obtained was recrystallized from ethanol to give (VIIIa) as yellow crystals m.pt. 242–3°C (yield 65%). (Found : C, 73.20; H, 4.10; N, 22.50: $C_{19}H_{13}N_5$ requires C, 73.31; H, 4.18; N, 22.50). IR : 2220 (C≡N) and 1595 cm^{-1} (C=N and C=C).

8-Cyano-3-Isopropyl-5-Methyl-7-Phenyl-*s*-Triazolo [4,3-c] Pyrimidine (VIIIb)

This compound was prepared in the manner described for (VIIIa) in 57% yield and recrystallized from butanol to give (VIIIb) as yellow crystals m.pt. 235–6°C. (Found : C, 69.20; H, 5.40; N, 25.30; $C_{16}H_{15}N_5$ requires C, 69.31; H, 5.41; N, 25.27). IR : 2980 (CH aliphatic), 2220 (C≡N) and 1620 cm^{-1} (C=N and C=C).

Formation of (IXab)

A mixture of (Ib) (0.01 mole) and ethyl cyanoacetate or malononitrile

(0.04 mole) in DMF (30 mL) was refluxed for 3 hrs. The solid obtained on dilution with water was filtered off and recrystallized from the proper solvent to give (IXa,b) as yellow crystals respectively.

Compound (IXa). m.pt. 235–6°C (ethanol), (yield 62%), (Found: C, 66.40; H, 4.60; N, 18.50; $C_{17}H_{14}N_4O_2$ requires C, 66.66, H, 4.57; N, 18.30). IR : 2980 (CH aliphatic), 2220 (C≡N) and 1810 cm^{-1} (C=O).

Compound (IXb). m.pt. 210–211°C (ethanol), (yield 55%) (Found : C, 69.50; H, 3.50; N, 27.00; $C_{15}H_9N_5$ requires C, 69.49, H, 3.47; N, 27.02). IR : 2220 (C≡N) and 1600 cm^{-1} (C=N and C=C). H^1 nmr (DMSO-d_6) δ 2.5 (s, 3H, CH_3), δ 2.9 (s, 1H, CH) and δ 7.6 ppm (m, 5H, aromatic protons).

Reaction of (Ib) with Aromatic Amines

A mixture of Ib (0.01 mole) and *p*-toluidine or *p*-anisidine (0.012 mole) in 20 mL of 20% aqueous NaOH was stirred at room temp. for 2 hrs. The solid obtained was filtered off and recrystallized from the proper solvent to give (IXc,d) as yellow crystals respectively.

Compound (IXc). m.pt. 195–6°C (ethanol), (yield 75%), (Found: C, 75.80; H, 5.50: N, 18.50; $C_{19}H_{16}N_4$ requires C, 76.00; H, 5.33; N, 18.66). IR : 3340 (NH), 2220 (C≡N) and 1610 cm^{-1} (C=N and C=C). H^1 nmr (DMSO-d_6) δ 2.2 (s, 3H, C_2–CH_3), δ 3.2 (s. 3H, pH–CH_3), δ 7.5 (m, 9H, aromatic protons) and δ 9.4 ppm (s, 1H, NH).

Compound (IXd). m.pt. 230–1°C (acetic acid), (yield 72%). (Found : C, 71.90; H, 4.90; N, 17.60; $C_{19}H_{16}N_4O$ requires C, 72.15, H, 5.06; N, 17.72). IR : 3200 (NH) and 2220 cm^{-1} (C≡N).

4-Phenyl-1-[4′-Chloro-5-′Cyano-6′-Phenylpyrimidin-2′-yl] Butadiene (IXe)

A mixture of (Ib) (0.01 mole) and cinnamaldehyde (0.015 mole) in absolute ethanol (30 mL) was treated with conc. HCl (1 mL) and refluxed for 3 hrs. The solid obtained was recrystallized from acetic acid to give (IXe) as yellow crystals m.pt. > 290°C (yield 82%). (Found : C, 72.00; H, 4.00; N, 13.50; $C_{21}H_{14}N_3Cl$ requires C, 72.10; H, 4.00; N, 13.73). IR : 2980 (CH aliphatic), 2220 (C≡N) and 1610 cm^{-1} (C=N and C=C).

4-Ethylthio-5-Cyano-2-Methyl-6-Phenylpyrimidine (IXg)

A mixture of (IXf) (0.01 mole) and ethyl iodide (3 mL) in ethanolic NaOH (10%, 50 mL) was refluxed for 2 hrs. The solid obtained was filtered off and recrystallized from ethanol to give (IXg) as colourless crystals, m.pt. 92.3°C (yield 82%). (Found : C, 64.30; H, 5.00; N, 18.50; $C_{14}H_{13}N_3S$ requires C, 64.36; H, 4.98; N, 18.39). IR : 2980 (CH aliphatic) 2220 (C≡N) and 1720 cm^{-1} (C=O).

4-(Carbethoxymethylthio)-5-Cyano-2-Methyl-6-Phenylpyrimidine (IXh)

A mixture of (IXf) (0.01 mole) and ethyl chloroacetate (0.012 mole) in ethanolic NaOH (10%, 50 mL) was refluxed (steam-bath) for 1 hr. The reaction mixture was poured onto cold water and neutralized with dil HCl. The solid obtained was filtered off and recrystallized from dil ethanol to give (IXh) as yellow crystals m.pt. 115–6°C (yield 85%). (Found: C, 60.00; H, 4.90; N, 15.10; $C_{16}H_{15}N_3SO_2$ requires C, 60.18; H, 4.70; N, 15.04). IR: 2980 (CH aliphatic), 2220 (C≡N) and 1720 cm^{-1} (C=O).

4-(Benzoylmethylthio)-5-Cyano-2-Methyl-6-Phenylpyrimidine (IXi)

A mixture of (IXf) (0.01 mole) and phenacyl bromide (0.012 mole) in absolute ethanol (30 mL) was refluxed for 2 hrs. The solid obtained was filtered off and recrystallized from ethanol to give (IXi) as yellow crystals m.pt. 122–3°C (yield 68%). (Found: C, 68.50; H, 4.30; N, 13.80; $C_{20}H_{15}N_3SO$ requires C, 68.37; H, 4.27; N, 13.67). IR: 2220 (C≡N) and 1680 cm^{-1} (C=O).

4-(β-Cyanoethylthio)-5-Cyano-2-Methyl-6-Phenylpyrimidine (IXj)

A solution of (IXf) (0.01 mole), pyridine (30 mL), water (10 mL) and acrylonitrile (3 mL) was refluxed for 3 hrs, cooled and diluted with water. The solid obtained was filtered off and recrystallized from dil. ethanol to give (IXj) as yellowish crystals, m.pt. 105–6°C (yield 76%). Found: C, 64.50; H, 4.30; N, 20.10; $C_{15}H_{12}N_4S$ requires C, 64.28; H, 4.28 N, 20.00). IR: 2980 (CH aliphatic), 2220 (C≡N) and 1584 cm^{-1} (C=N and C=C).

3-Cyano-2-[5′-Cyano-2′-Methyl-6′-Phenylpyrimidin-4′-ylthio]-4,6-dimethyl-pyridine (XIII)

A mixture of (IXf) (0.01 mole) in 20 mL of 25% aqueous NaOH and (XI) (0.01 mole) in DMSO (50 mL) was heated on water-bath for 1 hr. The reaction mixture was cooled, diluted with water and neutralized with dil acetic acid. The solid obtained was filtered off and recrystallized from ethanol to give (XIII) as yellow crystals, m.pt. 261-2° (yield 85%), (Found: C, 67.30; H, 4.00; N, 1970; $C_{20}H_{14}N_5S$ requires C, 67.41; H, 3.93; N, 19.66). IR: 2220 (C≡N) and 1590 cm^{-1} (C=N and C=N).

4-Phenyl-1-[5′-Cyano-2′-Methyl-6′-Phenylpyrimidin-4′-ylthio] Phthalazine (XIV)

This compound was prepared in the same manner described for (XIII) in yield 92% and recrystallized from ethanol to give XIV as yellow crystals, m.pt. 200–1°C (Found: C, 72.20; H, 4.00; N, 16.20; $C_{26}H_{17}N_5S$ requires C, 72.38; H, 3.94; N, 16.24).

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