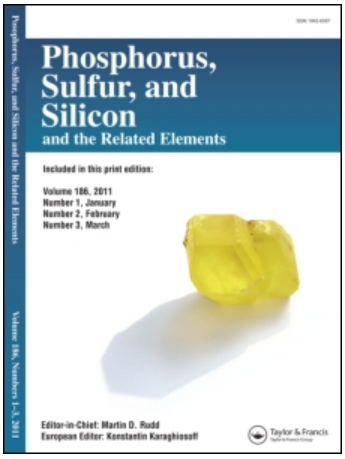

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Shalini Shukla[a]; Swati[a]; L. Prakash[a]
[a] Department of Chemistry, University of Rajasthan, Jaipur, India

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SYNTHESIS, CHARACTERIZATION AND ANTIMICROBIAL EVALUATION OF THIONE AND DITHIONE DERIVATIVES OF PYRIDO[2,3-*d*]PYRIMIDINES

SHALINI SHUKLA, SWATI and L. PRAKASH†
Department of Chemistry, University of Rajasthan, Jaipur-302004, India

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Synthesis of some newer pyrido[2,3-*d*]pyrimidine derivatives was carried out by the condensation of 2-amino-3-cyano-4,6-disubstituted pyridine with different arylisothiocyanates, thiourea and carbon disulfide. The compounds, thus obtained were put to elemental and physical analyses and were tested for antimicrobial activities.

Key words: Pyrido[2,3-*d*]pyrimidine thiones; pyrido[2,3-*d*]pyrimidine dithiones; ^{1}H NMR and IR.

INTRODUCTION

A perusal of the literature revealed the manifold implications[1-8] of pyrido[2,3-*d*]pyrimidine derivatives. These could be attributed to the presence of the toxophoric NCS moiety. Pyridopyrimidines bear close structural relationship with quinazolines and pteridines which are well known diuretic drugs. Therefore, these compounds were synthesized and evaluated for antimicrobial activity. The structure assignments were done on the basis of elemental analyses, IR and ^{1}H NMR studies (Table I).

RESULTS AND DISCUSSION

The reported compounds 4-imino-3,5,7-trisubstituted-pyrido[2,3-*d*]-pyrimidine-2(1H)thiones (II), 4-amino-5,7-disubstituted-pyrido[2,3-*d*]-pyrimidine-2(1H)thiones (III), and 5,7-disubstituted-pyrido[2,3-*d*]-pyrimidine-2,4(1H,3H)dithiones (IV) were synthesized by condensation of 2-amino-3-cyano-4,6-disubstituted-pyridine (I) with different arylisothiocyanates: thiourea and carbon disulfide, respectively (Scheme).

All the synthesized compounds were found to be active against the bacteria *S. aureus* and *E. coli* and against the fungi, *A. flavus, A. niger, F. moniliformae*, and *C. lunata*. All the newly synthesized compounds were obtained as colored solids and were soluble in DMSO.

SPECTRAL STUDIES

The important features of the spectral results are given below.

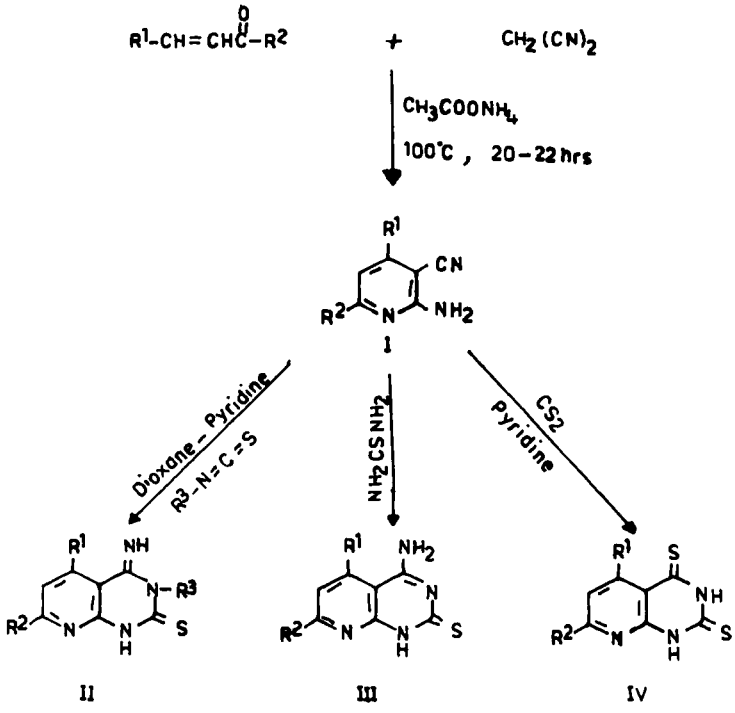
†Author to whom correspondence may be addressed.

TABLE I

Physical and analytical data of the compounds (IIa–IVc)

Compound No.	R^1	R^2	R^3	M.P.	Yield (%)	Molecular formula	Elemental Analysis (%) Found (Calcd.) C	H	N	S
IIa	C_6H_5	3,4-$(CH_3O)_2C_6H_3$	4-$CH_3C_6H_4$	278-80	68	$C_{28}H_{24}N_4O_2S$	70.10	5.09	11.60	6.63
							(70.00)	(5.00)	(11.67)	(6.67)
IIb	C_6H_5	3,4-$(CH_3O)_2C_6H_3$	2-$CH_3C_6H_4$	267-69	65	$C_{28}H_{24}N_4O_2S$	70.09	5.05	11.62	6.64)
							(70.00)	(5.00)	(11.67)	(6.67)
IIc	C_6H_5	3,4-$(CH_3O)_2C_6H_3$	4-$CH_3OC_6H_4$	271-72	70	$C_{28}H_{24}N_4O_3S$	67.78	4.89	11.25	6.44
							(67.74)	(4.84)	(11.29)	(6.45)
IId	4-ClC_6H_4	4-$CH_3OC_6H_4$	4-$CH_3C_6H_4$	246-48	69	$C_{27}H_{21}ClN_4OS$	66.89	4.40	11.51	6.58
							(66.87)	(4.33)	(11.56)	(6.60)
IIe	4-ClC_6H_4	4-$CH_3OC_6H_4$	2-$CH_3C_6H_4$	301-02	66	$C_{27}H_{21}ClN_4OS$	66.90	4.38	11.50	6.59
							(66.87)	(4.33)	(11.56)	(6.60)
IIf	4-ClC_6H_4	4-$CH_3OC_6H_4$	4-$CH_3OC_6H_4$	287-89	71	$C_{27}H_{21}ClN_4O_2S$	64.77	4.24	11.09	6.37
							(64.73)	(4.20)	(11.12)	(6.39)
IIg	4-ClC_6H_4	4-FC_6H_4	4-$CH_3C_6H_4$	225-26	64	$C_{26}H_{18}ClFN_4S$	66.08	3.85	11.81	6.76
							(66.03)	(3.81)	(11.85)	(6.77)
IIh	4-ClC_6H_4	4-FC_6H_4	2-$CH_3C_6H_4$	239-41	62	$C_{26}H_{18}ClFN_4S$	66.09	3.87	11.80	6.75
							(66.03)	(3.81)	(11.85)	(6.77)
IIi	4-ClC_6H_4	4-FC_6H_4	4-$CH_3OC_6H_4$	210-12	68	$C_{26}H_{18}ClFN_4OS$	63.88	3.70	11.40	6.52
							(63.86)	(3.68)	(11.46)	(6.55)

IIj	4-ClC_6H_4	4-FC_6H_4	2-$CH_3OC_6H_4$	148-51	69	$C_{26}H_{18}ClFN_4OS$	63.91	3.70	11.42	6.54
							(63.86)	(3.68)	(11.46)	(6.55)
IIk	4-ClC_6H_4	4-FC_6H_4	2-FC_6H_4	178-81	63	$C_{25}H_{15}ClF_2N_4S$	62.99	3.20	11.71	6.70
							(62.96)	(3.15)	(11.75)	(6.72)
IIIa	C_6H_5	3,4-$(CH_3O)_2C_6H_3$	-	218-20	66	$C_{21}H_{17}N_3O_2S_2$	61.78	4.20	10.29	15.70
							(61.92)	(4.18)	(10.32)	(15.72)
IIIb	4-ClC_6H_4	3,4-$(CH_3O)_2C_6H_3$	-	234-36	62	$C_{21}H_{16}ClN_3O_2S_2$	57.10	3.64	9.49	14.49
							(57.08)	(3.62)	(9.51)	(14.50)
IIIc	3,4-$(CH_3O)_2C_6H_3$	4-FC_6H_5	-	251-53	62	$C_{21}H_{16}FN_3O_2S_2$	59.32	3.80	9.84	15.04
							(59.29)	(3.76)	(9.88)	(15.06)
IVa	C_6H_5	3,4-$(CH_3O)_2C_6H_3$	-	207-11	58	$C_{21}H_{18}N_4O_2S$	64.67	4.65	14.32	8.20
							(64.62)	(4.62)	(14.36)	(8.21)
IVb	4-ClC_6H_4	3,4-$(CH_3O)_2C_6H_3$	-	215-17	65	$C_{21}H_{17}ClN_4O_2S$	59.40	4.50	13.17	7.51
							(59.36)	(4.00)	(13.19)	(7.54)
IVc	3,4-$(CH_3O)_2C_6H_3$	4-FC_6H_4	-	242-43	67	$C_{21}H_{17}FN_4O_2S$	61.81	4.22	13.70	7.81
							(61.76)	(4.17)	(13.73)	(7.84)



SCHEME

IR Spectra

In the IR spectra of 2-amino-3-cyano-4,6-disubstituted-pyridines (I), a sharp band was found at 2220 cm^{-1} which was due to the presence of the —C≡N moiety. This band completely vanished from the spectra of the compounds (II), (III) & (IV) indicating that cyclization has taken place. The presence of three characteristic bands due to the NH_2 group in compounds (III) in the region of 3420–3320 cm^{-1}, and the disappearance of these bands from the spectra of (II) & (IV), further confirmed the completion of the reaction. Compounds (II) also exhibited an absorption band in the region of 3140–3100 cm^{-1} due to the >C=NH group. Besides these, the title compounds showed characteristic absorptions in the region of 1250–1190 cm^{-1} and 1580–1320 cm^{-1} which were due to >C=S and NHC=S, respectively. Bands due to R_1 and R_2 were observed all through the course of the reaction.

^1H NMR Spectra

The NMR spectra in DMSO-d_6 show that the resonances of the CH_3 and CH_3O protons occur as singlets at δ 2.25 and δ 3.85, respectively. In all the synthesized compounds a complex multiplet of phenyl protons was observed in the range δ 6.50–7.50. Proton signals for the NH_2 protons in compound (III) generally merged with the complex multiplet of the phenyl protons. The NH proton occurred as a singlet at δ 8.02–8.72. A singlet due to the >C=NH proton was observed in the

TABLE II

Antimicrobial activity of the synthesized compounds (IIa–IVc)

Test organism	Inhibition zone (mm)																
	IIa	IIb	IIc	IId	IIe	IIf	IIg	IIh	IIi	IIj	IIk	IIIa	IIIb	IIIc	IVa	IVb	IVc
Grampositive bacteria	8.2	9.0	8.7	8.4	11.5	12.1	12.2	15.7	16.4	14.3	17.6	8.5	9.8	11.2	9.0	9.2	10.2
S. aureus	(0.90)	(0.99)	(0.97)	(0.92)	(0.92)	(0.97)	(0.98)	(1.27)	(1.31)	(1.44)	(1.41)	(0.93)	(1.08)	(1.23)	(0.99)	(1.01)	(1.12)
Gram nagative bacteria	8.4	8.6	9.0	9.2	10.9	11.5	11.7	16.1	16.7	15.2	16.4	8.8	9.8	11.5	9.9	9.5	10.7
E.coli	(0.92)	(0.95)	(0.99)	(1.01)	(0.87)	(0.92)	(0.94)	(1.30)	(1.34)	(1.22)	(1.31)	(0.97)	(1.08)	(1.26)	(1.09)	(1.04)	(1.18)
Fungi	7.2	8.0	8.1	8.1	7.2	6.4	12.4	12.0	10.2	12.4	10.2	7.8	6.4	10.6	9.0	9.2	10.4
Aspergillus flavus	(0.88)	(0.97)	(0.99)	(0.93)	(0.83)	(0.73)	(1.55)	(1.50)	(1.27)	(1.55)	(1.27)	(0.92)	(0.75)	(1.25)	(1.06)	(1.08)	(1.22)
Aspergillus niger	8.1	8.0	7.8	6.5	6.4	7.4	8.1	8.2	9.2	7.8	6.6	7.7	7.2	8.2	7.6	6.9	10.2
	(0.95)	(0.94)	(0.92)	(0.72)	(0.71)	(0.82)	(0.99)	(1.00)	(1.12)	(0.95)	(0.78)	(0.90)	(1.18)	(0.96)	(0.86)	(0.81)	(1.20)
Fusarium moniliformae	7.4	7.7	7.6	6.1	6.2	7.0	7.5	7.0	8.4	7.2	8.6	6.4	6.6	7.6	6.4	7.4	6.8
	(0.92)	(0.96)	(0.95)	(0.72)	(0.73)	(0.82)	(0.94)	(0.87)	(1.00)	(0.90)	(1.00)	(0.74)	(0.70)	(0.88)	(0.74)	(0.86)	(0.79)
Curvularia lunata	7.0	7.5	8.0	7.4	6.1	6.9	7.0	9.0	12.6	12.8	8.9	7.1	10.4	8.0	7.9	6.8	7.6
	(0.79)	(0.84)	(0.90)	(0.92)	(0.76)	(0.86)	(0.80)	(1.03)	(1.45)	(1.47)	(1.11)	(0.88)	(1.30)	(1.00)	(0.98)	(0.85)	(0.95)

Values in parentheses represent activity index = inhibition area of the sample/inhibition area of the standard.

range δ 8.84–9.0, but sometimes it merged with the resonance of the >N—H proton.

The spectral studies are in the agreement with the structures proposed.

ANTIMICROBIAL ACTIVITY

Synthesized pyrido[2,3-*d*]pyrimidine thiones and dithiones were evaluated for their antimicrobial activity following the method of Gould *et al.*[9] using streptomycin in antibacterial and mycostatin in antifungal activity as the reference compound.

All the compounds showed activity against both the microorganisms viz. *Escherichia coli, Staphyloccoccus aureus* (bacteria) and *Aspergillus flavus, Aspergillus niger, Fusarium moniliformae, Curvularia lunata* (fungi). Fluorine-containing pyrido[2,3-*d*]-pyrimidine thiones and dithiones showed better activity than all the others which were found to be moderately activate. The results are recorded in Table II.

EXPERIMENTAL

Melting points were determined in open capillary tubes and are uncorrected. IR (KBr; max cm^{-1}) spectra were recorded on a Perkin-Elmer 577 grating spectrophotometer and ^1H NMR spectra in DMSO-d_6 on a Jeol FX90Q (90 MHz) using TMS as internal standard.

Synthesis of 4-imino-3,5,7-trisubstituted pyrido[2,3-d]pyrimidin-2(1H)-thiones (II). A mixture of I (0.01 mole), the appropriate isothiocyanate (0.01 mole), dioxane (15.0 ml) and pyridine (2.0 ml) was heated under reflux at 150°C for about 20–22 hr. After cooling, the contents of the flask were poured onto crushed ice with constant stirring to obtain a solid yellow mass which was washed with water followed by sodium bicarbonate (5% w/v) and finally with water. The dried crude product was recrystallized from glacial acetic acid.

Synthesis of 4-amino-5,7-disubstituted pyrido[2,3-d]pyrimidine-2(1H)-thione (III). A mixture of I (0.01 mole) and thiourea (0.02 mole) was heated on oil bath at 120–130°C for 2 hr with constant stirring. The temperature was raised to 180°C, and finally the mixture was heated at 230°C for 2 hr. The product obtained was washed with water followed by a saturated solution of sodium bicarbonate and finally with cold ethanol and recrystallized from DMF-EtOH (1:2).

Synthesis of 5,7-disubstituted pyrido[2,3-d]pyrimidine-2,4[1H,3H]-dithiones (IV). A mixture of I (0.01 mole) and carbon disulfide (0.04 mole) in 15 ml of pyridine was refluxed on water-bath for 10–15 hr. After cooling, the excess pyridine was removed by distillation under reduced pressure, and the residue was washed with water followed by saturated solution of sodium bicarbonate and finally with cold ethanol. The crude product was recrystallized from DMF-EtOH(1:2).

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