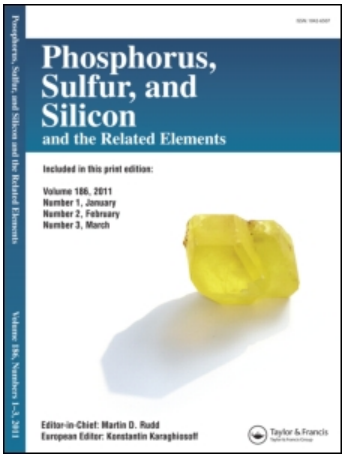

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CHEMISTRY AND CYCLIZATION REACTIONS OF 2-MERCAPTO-3-PHENYL PYRIMIDO THIENO[2,3-*b*]QUINOXALINONE DERIVATIVES

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Reaction of 2-mercapto-3-phenyl pyrimido[4′,5′:4,5]thieno[2,3,-*b*]quinoxalin-4-one(1) with hydrazine hydrate gives 2-hydrazino derivative (2) which undergoes ring closure reactions with formic acid, acetic anhydride, and benzoyl chloride to produce the S-triazolo derivatives(3–5). While treatment with nitrous acid gives the tetrazolo derivative (6). Reaction of (2) with acetylacetone, phthalic anhydride, and/or aromatic aldehydes affords, N-pyrazolyl- N-phthalazino- and N-arylidene derivatives (7–9) respectively. Compound (1) reacts with alkyl halides in basic medium to give the corresponding thioethers (10). Compound (1) reacts with diethyl bromomalonate to yield (11) which is transformed into (12a,b) under the influence of hydrazine or phenylhydrazine. Treatment of (1) with ethyl chloroacetate yields the thioester (13). Reaction of (1) with chloroacetamide or (13) with ammonia gave the same product. Hydrazinolysis of the thioester (13) gave the corresponding carbohydrazide (15) which reacts with acetylacetone, aromatic aldehydes, and phthalic anhydride to give the corresponding 2-(N-pyrazolyl, N-arylidene, and/or N-phthalazino) pyrimidothienoquinoxalin-4-ones (16–18). Oxidation of (1) by H_2O_2 either in dioxane or in NaOH gives either the corresponding disulfide or the pyrimidothienoquinoxalin-2,4-dione (19,20) respectively.

Keywords: Cyclization reactions; quinoxalones; NMR spectra; thioethers

Quinoxaline derivatives constitute an important class of biologically active compounds as antimicrobial, anticancer; and antileprous[1,4] agents. As a continuation of our interest in the study of the chemistry of quinoxaline derivatives[5,6]; the present investigation deals with the synthesis of certain novel pyrimidothienoquinoxaline derivatives.

Refluxing 2-mercapto-3-phenyl-pyrimido[4′,5′:4,5]thieno[2,3-*b*]quinoxalin-4-one (1) in ethanol with hydrazine hydrate gave the corresponding 2-hydrazino-

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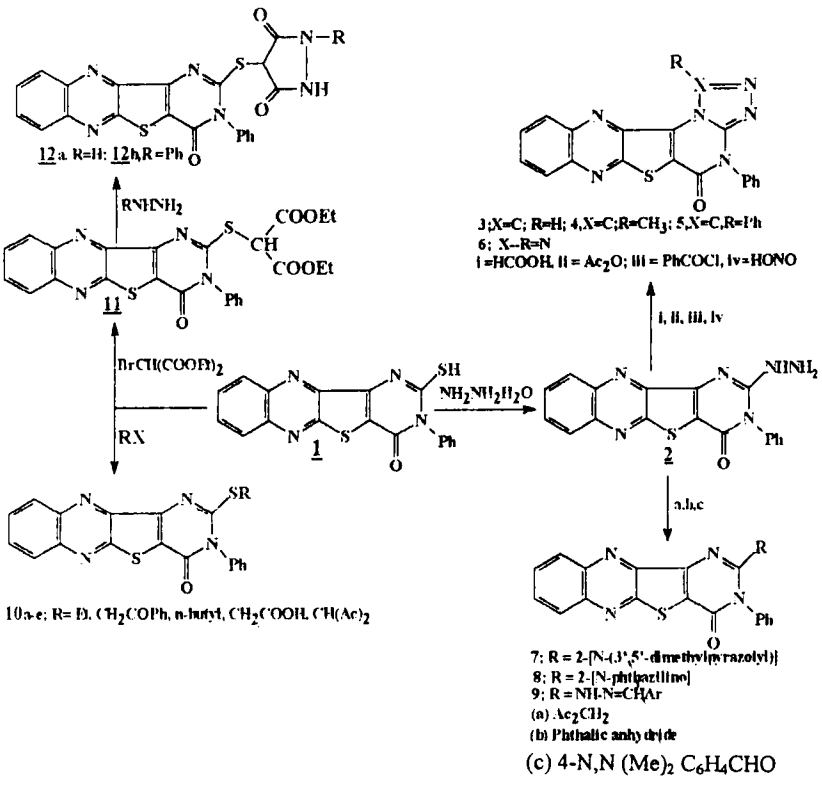
3-phenyl pyrimido thieno quinoxalinone (2). Compound (2) underwent several cyclization reactions. Treatment of (2) with formic acid; acetic anhydride or benzoyl chloride gave the corresponding substituted (R = H,CH_3, Ph) triazolopyrimidothienoquinoxalinone (3–5) while reaction with nitrous acid yielded tetrazolopyrimidothienoquinoxalinone (6). Treatment of (2) with acetylacetone led to formation of 2-(3,5-dimethylpyrazol-1-yl)-3-phenyl pyrimido[5′,4′:4,5] thieno[2,3-*b*]quinoxalin-4-one (7). Reaction of (2) with phthalic anhydride in acetic acid yielded (3-phenyl-4-oxo-pyrimido[4′,5′:4,5] thieno[2,3-b]quinoxalin-2-yl)phthalazin-1,4-(3H)dione (8). Compound (2) reacted with 4-N,N-dimethylbenzeldehyde in basic medium to give the corresponding 2-arylidene derivative (9). The mercapto compound (1) was transformed by reaction with alkyl or aralkyl halides in ethanolic solution containing anhydrous sodium acetate into the S-alkyl or S-aralkyl derivatives (10_{a-e}) (Scheme I). Compound (1) also reacted with diethyl bromomalonate in basic medium to give the S-alkylated product (11). Further, compound (11) reacted with hydrazine and phenyl hydrazine to give the S-pyrazolone derivatives ($12_{a,b}$). Treatment of (1) with ethyl chloroacetate in basic medium yielded 2-(ethoxycarbonylmethylthio)-3-phenylpyrimido[4′,5:4,5]thieno[2,3-*b*]quinoxalin-4-one (13), which when treated with ammonia gave the 2-(carboamidomethyl-thio) derivative (14). The same product was isolated by reaction of (1) with chloroacetamide. Reaction of the ester (13) with hydrazine hydrate in ethanol led to formation of the 2-thiomethylcarboxhydrazide derivative (15). The hydrazide (15) reacted with acetylacetone; aromatic aldehydes; and phthalic anhydride yielding the corresponding 2 (pyrazolyl, arylidene and/or phthalizino)-3-phenyl-pyrimido-[4′,5′:4,5]thieno[2,3-*b*]quinoxalin-4-one (16–18) respectively. Oxidation of the mercapto compound (1) by H_2O_2 either in acetic acid or in dioxane gave the disulfide derivative of the dimer (19). When (1) was refluxed in aqueous NaOH it gave 3-phenyl-pyrimido[4′.5′:4,5]thieno[2,3-*b*]quinoxalin-2,4-dione(20) (Scheme II). The physical data agrees with a compound described earlier[5]. The analytical, IR- and ^{1}H-NMR- spectra of the novel compounds agree with the assigned structures and are compiled in tables I and II.

EXPERIMENTAL

Melting points reported are uncorrected. IR spectra (Tables I and II) are recorded for potassium bromide wafers on a Pye Unicam SP 3100 Spectrophotometer; ^{1}H-NMR spectra (Tables I and II) are recorded in ($CDCl_3$) or (DMSO-d_6) on a Varian 90 or EM-390 M Hz Spectrometer using TMS as an internal standard.



SCHEME I

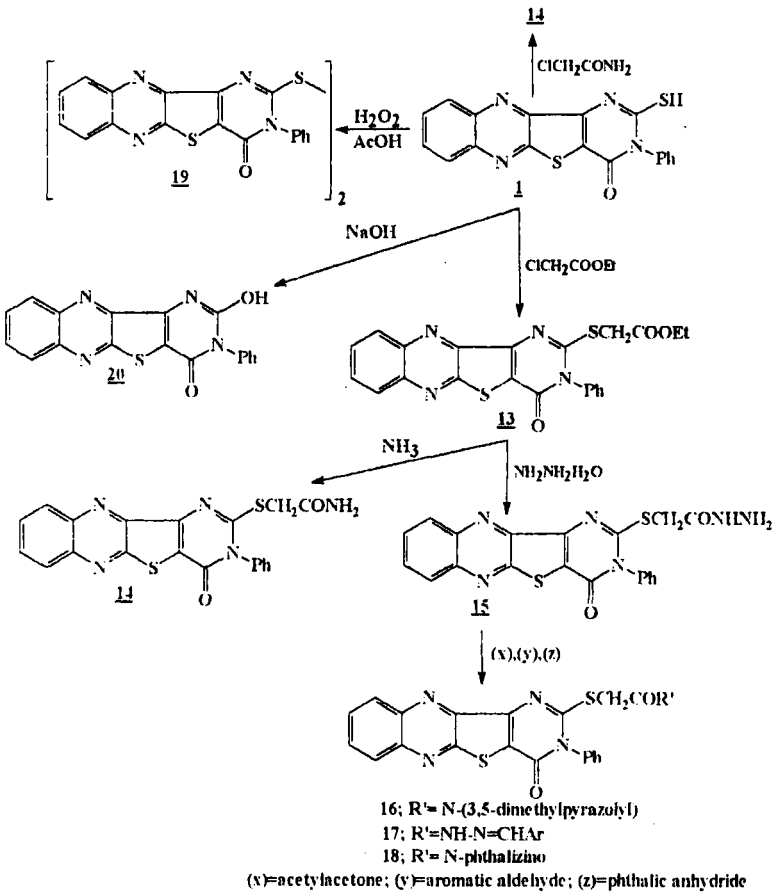
Elemental analysis, yields, melting points, and spectral data are given in tables I and II respectively.

2-Mercapto-3-phenyl-pyrimido[4',5' :4,5]thieno[2,3-b]quinoxalin-4-one (1)

was isolated as a yellow compound m.p 328–330°C (literature)[5] m.p 330°C.

2-Hydrazino-3-phenyl pyrimido[4',5' :4,5]thieno[2,3-b]quinoxalin-4-one (2)

was prepared by refluxing hydrazine hydrate (5 ml) with **1** (3.6 g, 0.01 mol) in absolute ethanol (30 ml) for 2 hr. The solid which separated on cooling was filtered and washed with ethanol to yield **2**.



SCHEME II

5-Phenyl-S-triazolo[3'',4'':2',3']pyrimido[4',5':4,5]thieno [2,3-b]-quinoxalin-6-one (3)

A mixture of **2** (0,72 g, 0.002 moL) and formic acid (10 ml) was refluxed for 4 hr. The solid which was isolated after addition of water to yield **3**

1-Methyl-5-phenyl-S-triazolo[3'',4'':2',3']pyrimido[4',5':4,5]thieno [2,3-b]-quinoxalin-6-one (4)

A mixture of **2** (3.6 g, 0.01 mol) and acetic anhydride (25 ml) was refluxed for 3 hr. Compound (4) precipitated upon cooling.

TABLE I Elemental Analysis and Spectral Data of Compounds 1–10

Compound No.	*Yield% Colour*	*M.P C Solvent*	*Formula Mol. wt*	*Analysis Calcd./Found*				*Spectral data IR(KBr) cm^{-1}/^{1}H-NMR*
				C	*H*	*N*	*S*	
1	65	330	$C_{18}H_{10}N_4OS_2$	59.66	2.67	15.46	17.67	(NH)3100, (CO)1690,(C=S)1210
	yellow	ethanol	362	59.43	2.80	15.60	17.58	^{1}H-NMR(DMSO):δ7.8–8.5(m, 9H, arom.), and δ 9.8(1H(NH).
2	85	325	$C_{18}H_{12}N_6OS$	60.00	3.33	23.33	8.88	($NHNH_2$)3200–3350, (CO)1680.
	Pale yellow	ethanol	360	59.81	3.21	23.42	8.72	
3	70	>360	$C_{19}H_{10}N_6OS$	61.62	2.70	22.60	8.64	(CO)1690, (C=N−)1590.
	yellow	acetic acid	370	61.47	2.58	23.00	8.50	^{1}H NMR($CDCl_3$), δ 7.5–8.5(m, 9H, arom.), and δ 10.2(s, 1H, CH).
4	80	312	$C_{20}H_{12}N_6OS$	62.50	3.12	21.87	8.33	(CH) aliph.) 3000; (CO)1670.
	yellow	acetic acid	384	62.31	3.20	21.70	8.11	^{1}H NMR(DMSO), δ 2.8(s, 3H, CH_3); and δ 7.9–8.6(m, 9H, arom.).
5	78	345	$C_{25}H_{14}N_6OS$	67.26	3.13	18.83	7.17	(CO)1700, (C=N−)1600–1620
	green-yellow	acetic acid	446	66.98	3.00	18.60	7.30	^{1}H NMR(TFA), and δ·7.7–8.5(m, 14H, atom.)
6	65	321–322	$C_{18}H_9N_7OS$	58.22	2.42	26.41	8.62	(CO)1680, (C=N−)1620.
	pale-yellow	ethanol	371	58.00	2.34	26.35	8.48	^{1}H NMR($CDCl_3$), and δ 7.4–7.8(m, 9H, arom.).
7	70	300–303	$C_{23}H_{16}N_6OS$	65.09	3.77	19.81	7.54	(CO)1680, (C=N−)1600.
	yellowish	ethanol	424	64.88	3.62	19.73	7.42	^{1}H NMR($CDCl_3$), δ 2.3(s, 6H, Two CH_3), δ 7.3–8.2(m, 9H, arom.),and δ 8.5(1H, CH).

TABLE I Continued

Compound No.	*Yield% Colour*	*M.P C Solvent*	*Formula Mol. wt*	*Analysis Calcd./Found* *C*	*H*	*N*	*S*	*Spectral data IR(KBr) cm^{-1}/^{1}H-NMR*
8	80	292	$C_{26}H_{14}N_6O_3S$	63.67	2.58	17.14	6.53	(NH)3150, (three CO) 1840, 1740, 1680.
	yellow	acetic acid	490	63.50	2.69	17.23	6.43	
9	85	296	$C_{27}H_{21}N_7OS$	65.89	4.27	19.95	6.50	(NH)3350, (CO)1690, (C=N−)1610.
	orange	ethanol	491	65.68	4.13	19.82	6.42	
10_a	70	240–41	$C_{20}H_{14}N_4OS_2$	61.53	3.58	14.35	16.41	(CO)1680, (-C=N−)1590.
	pale orange	ethanol	390	61.38	3.56	14.27	16.29	
10_b	85	260	$C_{26}H_{16}N_4O_2S_2$	65.00	3.33	16.66	13.33	Two(CO)1730, 1680, (C=N−)1620.
	yellow	ethanol	480	64.86	3.21	16.57	13.12	^{1}H NMR(DMSO), δ 4.8(s, 2H, CH_2), and δ 7.5–8.2(m, 14H, arom.).
10_c	65	228	$C_{22}H_{18}N_4OS_2$	63.15	4.30	13.39	15.31	(CO)1680, (C=N−)1630.
	whitish	ethanol	418	62.96	4.23	13.26	15.29	^{1}H NMR($CDCl_3$), δ 0.8–1.2(t, 3H, CH_3), δ 1.4–1.7[$4H_2(CH_2)_2$],δ 3.2–3.5(2H, CH_2), and δ 7.7–8.1(9H, arom.).
10_d	75	332	$C_{20}H_{12}N_4O_3S_2$	57.14	2.85	13.33	15.23	(CH aliph.) 3000, (CO)1680–1710, (C=N−)1620.
	orange	ethanol	420	57.00	2.77	13.20	15.08	^{1}H-NMR($CDCl_3$), δ 4.2(s, 2H, CH_2), δ 6.4(1H, OH), and δ 7.4–8.1(m, 9H, arom.).
10_e	68	278	$C_{23}H_{16}N_4O_3S_2$	60.00	3.47	12.17	13.19	(CO) 1670–1710, (C=N−)1610.
	green-yellow	acetic acid	460	59.83	3.51	12.00	13.10	^{1}H-NMR($CDCl_3$), δ 2.3(s, 6H, $(CH_3)_2$), δ 3.1(s, 1H, CH),and δ 7.5–8.3(m, 9H, arom.

TABLE II Elemental Analyses and Spectral Data of Compounds 11–20.

Compound No.	*Yield % Colour*	*M.P C Solvent*	*Formula Mol. wt*	*Analysis Calcd./Found* *C*	*H*	*N*	*S*	*Spectral data IR(KBr) cm^{-1}/^{1}H-NMR*
11	85	221	$C_{25}H_{20}N_4O_5S_2$	57.69	3.84	10.76	12.30	(CH alephatic) 2980, (Two CO, ester)1710-1740, (CO)1680.
	redish	ethanol	520	57.52	3.76	10.66	12.21	^{1}H NMR($CDCl_3$), δ 1.3–1.6, (t, 6H, $(CH_3)_2$), δ 4.2–4.5(q, 4H, $2CH_2$), δ 5.1 (s, 1H, CH) and δ 7.5–8.5 (m, 9H, arom.)
12_a	75	342	$C_{21}H_{12}N_6O_3S_2$	54.78	2.60	18.26	13.61	(NH) 3200–3300, (CO) 1660–1690.
	lemon-yellow	ethanol	460	54.70	2.53	18.10	13.52	
12_b	70	>360	$C_{27}H_{16}N_6O_3S_2$	60.44	2.98	15.67	11.94	(NH) 3300–3400, (CO) 1660–1700.
	yellow	ethanol	536	60.33	2.89	15.43	11.85	^{1}H NMR (DMSO), δ 7.4–8.2(m, 14H, arom.), δ 9.1 1H(CH), and δ 10.5 (s, 1H, NH).
13	90	245	$C_{22}H_{16}N_4O_3S_2$	58.92	3.57	12.50	14.28	(CO ester) 1720, (CO) 1680
	pale-yellow	ethanol	448	58.78	3.48	12.61	14.30	^{1}H NMR ($CDCl_3$) δ 1.3–1.6(t, 3H, CH_3), δ 1.2–1.4(q, 2H, CH_2), δ 4.1(s, 2H, CH_2) and δ 7.3–8 (m, 9H, arom.).
14	65	293	$C_{20}H_{13}N_5O_2S_2$	57.27	3.10	16.70	15.27	(NH_2) 3200–3350, (CO) 1680, (CO) 1660.
	buff	ethanol	419	57.18	3.00	16.63	15.16	

TABLE II Continued

Compound No.	*Yield % Colour*	*M.P C Solvent*	*Formula Mol. wt*	*Analysis Calcd./Found* *C*	*H*	*N*	*S*	*Spectral data IR(KBr) cm^{-1}/^{1}H-NMR*
15	85	270	$C_{20}H_{14}N_6O_2S_2$	55.29	3.32	19.35	14.74	($NHNH_2$) 3150–3240, (CO) 1710, (CO) 1680.
	redish	acetic acid	434	55.12	3.24	19.23	14.62	
16	70	290	$C_{25}H_{18}N_6O_3S_2$	60.24	3.61	16.85	12.85	Two (CO) 1680, 1710, (C=N-) 1600.
	yellowish	ethanol	498	60.00	3.53	16.72	12.90	^{1}H-NMR ($CDCl_3$), δ 2.4(s, 3H, CH_3), δ 2.8(s, 3H, CH_3),δ 4.2(s, 2H, CH_2), δ 6.1 (s, 1H, CH) and δ 7.5–8.3 (m, 9H, arom.).
17	78	221	$C_{29}H_{23}N_7O_3S_2$	61.59	4.07	17.34	11.32	(NH) 3200, (CO) 1660–1700.
	orange	ethanol	565	61.43	4.12	17.20	11.21	
18	70	65–66	$C_{28}H_{16}N_6O_4S_2$	59.57	2.83	14.89	11.34	(NH) 3200, (CO phthalazine) 1790, 1730, (CO) 1680,(C=N-) 1620.
	yellow	acetic acid	564	59.42	2.76	14.75	11.25	^{1}H-NMR (DMSO) δ 4.7(s, 2H, CH_2), δ 7.4–8.1 (m, 13H, arom.),and δ 8.9(s, 1H, NH).
19	82	>360	$C_{36}H_{18}N_8O_2S_4$	59.83	2.49	15.51	17.72	(CO) 1680, (C=N-) 1610.
	lemon-yellow	ethanol	722	59.80	2.42	15.40	17.61	^{1}H-NMR (DMSO), and δ 7.3–8.4(m, 18H, arom.).
20	80	327–28	$C_{18}H_{10}N_4O_2S$	62.42	2.89	16.18	9.24	(NH) 3200, two(CO) 1740–1670.
	yellow	acetic acid	346	62.28	2.75	16.00	9.47	^{1}H-NMR(DEMSO), δ 7.4–8(m, 9H, arom.), and δ 9.1(s, 1H, NH).

1,5-Diphenyl-S-triazolo[3",4":2',3']pyrimido[4',5':4,5]thieno [2,3-b]-quinoxalin-6-one (5)

A mixture of **2** (1.8 g, 0.05 mol) and benzoyl chloride (15 ml) was refluxed for 5 hr. The solid which separated was filtered and washed by pet-ether.

5-Phenyl-S-tetrazolo[3",4":1',6']pyrimido[4',5':4,5]thieno [2,3-b]quinoxalin-6-one (6)

was prepared by treatment of **2** (3.6 g, 0.01 mol) and hydrochloric acid while dropping sodium nitrite solution (10 ml) at 0°C and stirred for 30 minutes. Compound **6** precipitated upon cooling.

3-Phenyl-2 (3,5-dimethyl-pyrazol-1-yl)pyrimido[4',5':4,5]thieno [2,3-b]quinoxalin-4-one (7)

A mixture of **2** (3.6 g, 0.01 mol) and acetylacetone (0.005 mol) in ethanol (20 ml) was refluxed for 4 hr. After cooling, compound **7** which separated by filteration.

2-(3,4-Dihydro-3-phenylpyrimido[4',5':4,5]thieno [2,3-b]quinoxalin-4-one)phthalazin-1,4(3H)dione (8)

A mixture of **2** (0.62 g, 0.002 mol) and phthalic anhydride (0.296 g, 0.002 mol) in acetic acid (15 ml) was refluxed for 3 hr. Compound **8** precipitated on cooling.

3-Phenyl-2-arylidinehydrazonopyrimido[4',5':4,5]thieno [2,3-b]quinoxalin-4-one (9)

A mixture of **2** (0.76 g, 0.002 mol) and *p*-N,N-dimethylbenzaldehyde (0.002 mol) in ethanol (15 ml) and a few drops of piperidine was refluxed for 3 hr. The solid **9** was isolated after cooling.

3-Phenyl-2-alkylthio pyrimido[4',5':4,5]thieno[2,3-b]quinoxalin-4-one (10_{a-e})

A mixture of an alkyl halide (ethyl iodide, phenacyl bromide, n-butyl bromide, chloroacetic acid or chloro acetylacetone (0.012 mol) and **1** (3.62 g, 0.01 mol)

dissolved in absolute ethanol (20 ml) containing anhydrous sodium acetate was refluxed for 1 hr and cooled. Compounds **10a–e** precipitated.

2-(Diethoxycarbonylmethyl thio)-3-phenyl-pyrimido[4',5':4,5]thieno[2,3-b]quinoalin-4-one (11)

A mixture of **1** (3,62 g, 0.01 mol) and diethyl bromomalonate (2.39 g, 0.01 mol) was refluxed in ethanol (40 ml) in the presence of anhydrous sodium acetate for 1 hr. Upon concentration, compound (11) precipitated.

3-Phenyl-2-[[3,5-dioxo-1(H)(phenyl)pyrazol-4''-yl thio]pyrimido [4',5':4,5]-thieno[2,3-b]quinoxalin-4-one ($12_{a,b}$)

A mixture of **11** (2.6 g, 0.005 mol) and hydrazine hydrate or phenyl hydrazine (0,005 mol) was refluxed for 3 hr. in abs. ethanol (20 ml) and cooled to precipitate 12a and 12b.

3-Phenyl-2-(ethoxycarbonylmethylthio)-pyrimido [4',5':4,5] thieno [2,3-b]-quinoxalin-4-one (13)

A mixture of **1** (3.62 g, 0.01 mol), ethyl chloroacetate (1.22 g, 0.01 mol) and anhydrous sodium acetate (5 gm) in ethanol (80 ml) was refluxed for 3 hr. The solid **13** was isolated after the addition of water.

3-Phenyl-2-(carboamidomethylthio)-pyrimido [4',5':4,5]thieno[2,3-b]quinoxalin-4-one (14)

To a solution of **13** (2.24 g, 0.005 mol) in ethanol (40 ml) an ammonia solution (20 ml) was added and the reaction mixture was kept at room temperature for 2 days. The precipitate was recrystallized and analysed as given in (Table II). The same product was also obtained by a different method by refluxing **1** with chloroacetamide.

3-Phenyl-2-(thiomethylcarboxhydrazide)-pyrimido [4',5':4,5]thieno[2,3-b]quinoxalin-4-one (15)

A mixture of **13** (2.24 g, 0.005 mol) and excess hydrazine hydrate 95% (3 ml) in abs. ethanol (40 ml) was refluxed for 2 hr. After cooling the solid product was filtered off to give **15**.

3-Phenyl-2-[3,5-dimethyl-pyrazol-1-yl-carbomethyl thio]pyrimido[4',5':4,5]thieno-[2,3-b]quinoxalin-4-one (16)

A mixture of **15** (2.17 g, 0.005 mol) and acetylacetone (0.005 mol) in ethanol was heated under reflux for 2 hr. The precipitate which formed on cooling was filtered off to give **16**.

3-Phenyl-2-(thiomethylcarboxarylidinehydrazide)-pyrimido [4',5':4,5]-thieno[2,3-b]quinoxalin-4-one (17)

A mixture of **15** (2.17 g, 0.005 mol) and *p*-N,N-dimethylbenzaldehyde (0.005 mol) in ethanol (40 ml) and a few drops of piperidine was refluxed for 3 hr. The product collected after cooling and filtration was **17**.

2-[3,4-Dihydro-3-phenyl-pyrimido[4',5':4,5]thieno [2,3-b]quinoxalin-4-one]-phthalazin-1,4(3H)dione (18)

A mixture of **15** (4.34 g, 0.01 mol) and phthalic anhydride (1,48 g, 0.01 mol) in acetic acid (30 ml) was refluxed for 3 hr. Compound 18 was isolated after addition of water.

Bis[3-phenyl-pyrimido[4',5':4,5]thieno[2,3-b]quinoxalin-4-one]sulphide (19)

A mixture of **1** (3.62 g, 0.01 mol) and H_2O_2 (20 ml) in acetic acid 30 ml was stirred for 2 hr. The solid was separated by filteration.

3-Phenylpyrimido[4',5':4,5]thieno[2,3-b]quinoxalin-2,4-(1H)dione (20)

A mixture of **1** (2.62 g, 0.01 mol) and NaOH (20%, 30 ml) was refluxed for 2 hr. The reaction mixture was cooled to room temperature and neutralized by HCl. The solid product was in agreement with an authentic sample[5].

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