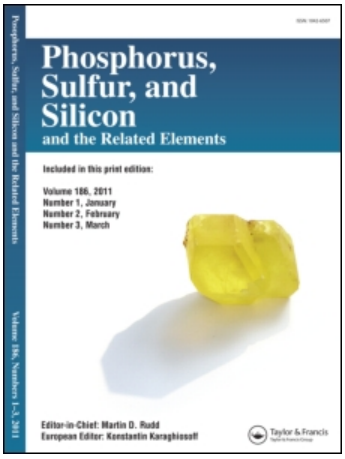

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SYNTHESIS AND ANTIBACTERIAL ACTIVITIES OF SOME NEW THIENO-[2,3-b]QUINOLINES

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SYNTHESIS AND ANTIBACTERIAL ACTIVITIES OF SOME NEW THIENO-[2,3-b]QUINOLINES

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3-Cyanoquinoline-2(1H)-thione (**1**) was reacted with some halocompounds to give S-substituted thioquinoline derivatives **2**, **6** and **7**. Cyclization of **7** yielded thienoquinoline **8**. Also, reaction of **1** with chloroacetone, chloroacetonitrile, ethyl chloroacetate and chloroacetamide furnished thienoquinolines **3**, **4**, **5** and **8**, respectively. Moreover, compounds **4** and **8** underwent different sequence reactions to give some new pyrimido- and triazino-[4′,5′:4,5]thieno[2,3-b]quinoline derivatives (**9**–**21**). Most of the prepared compounds were screened *in vitro* for their antibacterial activities.

Key words: Thienoquinolines; pyrimidiothienoquinolines and triazinothienoquinolines.

INTRODUCTION

The quinoline ring structures are important in medicinal plant alkaloids[1] and as a consequence have found application in chemotherapy. Thus some quinoline derivatives were found active as antimalarial, antifilarial and hypotensive agents.[2–5] Related 4-aminoquinolines have recently been described as potential analgesics, antipyretics, antiinflammatories and antirheumatics.[6] Also, other quinoline derivatives are reported to be useful as bactericides,[7] fungicides[8] and insecticides.[9,10] We have, therefore, synthesized the title compounds which might show enhanced biological activity due to the presence of an additional thiophene moiety.

RESULTS AND DISCUSSION

The present paper deals with the synthesis of some new thieno[2,3-b]quinoline derivatives and study the antibacterial activity of most of them.

Our approach to the synthesis of the desired compounds started from 3-cyanoquinoline-2(1H)-thione (**1**) which was prepared according to the previous method by reaction of 2-chloro-3-cyanoquinoline with thiourea in refluxing methanol.[11] Treatment of **1** with ethyl iodide in the presence of sodium acetate led to thioether **2**.

Reaction of **1** with chloroacetone, chloroacetonitrile and/with ethyl chloroacetate by refluxing in ethanol containing excess amounts of fused sodium acetate gave 3-amino-2-substituted-thieno[2,3-b]quinolines (**3**, **4** and **5** respectively) in high yields, whereas reaction of **1** with chloroacetamide under the same (above) conditions yielded (3-cyano-2-quino-linylthio)acetamide (**7**). Compound **7** on heating in ethanol containing sodium ethoxide, underwent smooth cyclization into 3-amino-thieno[2,3-

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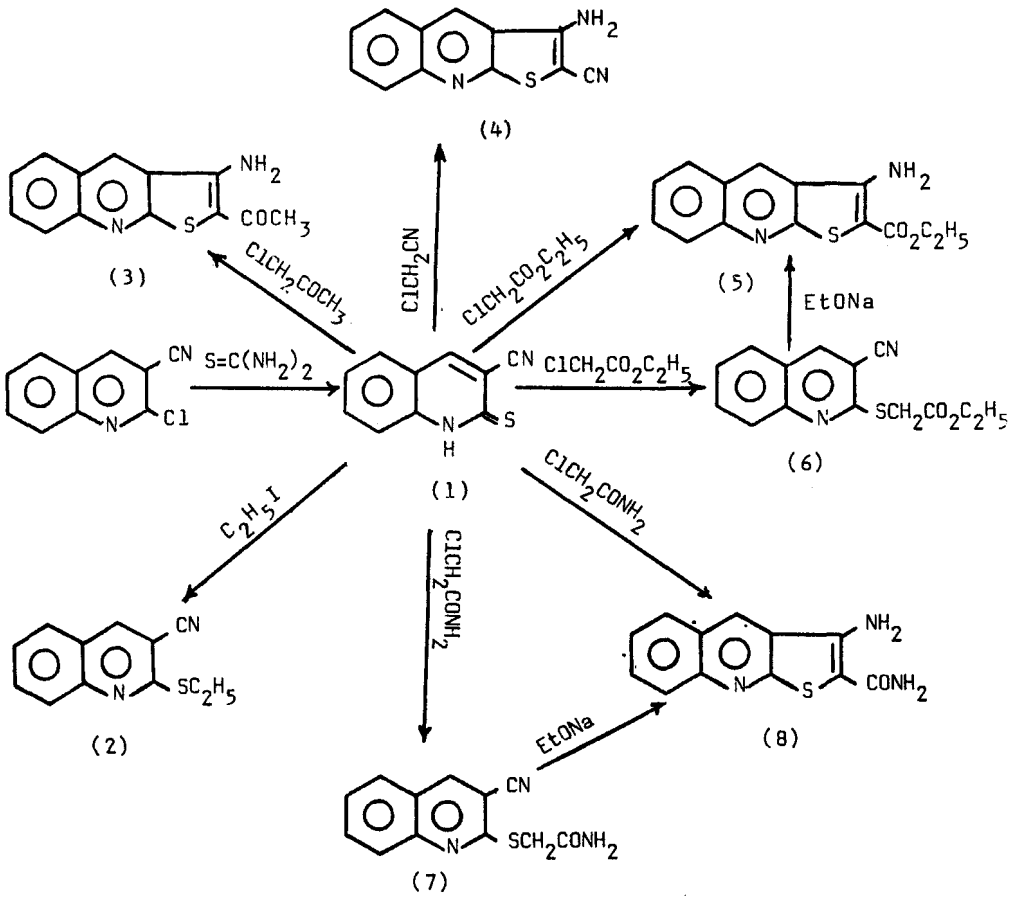
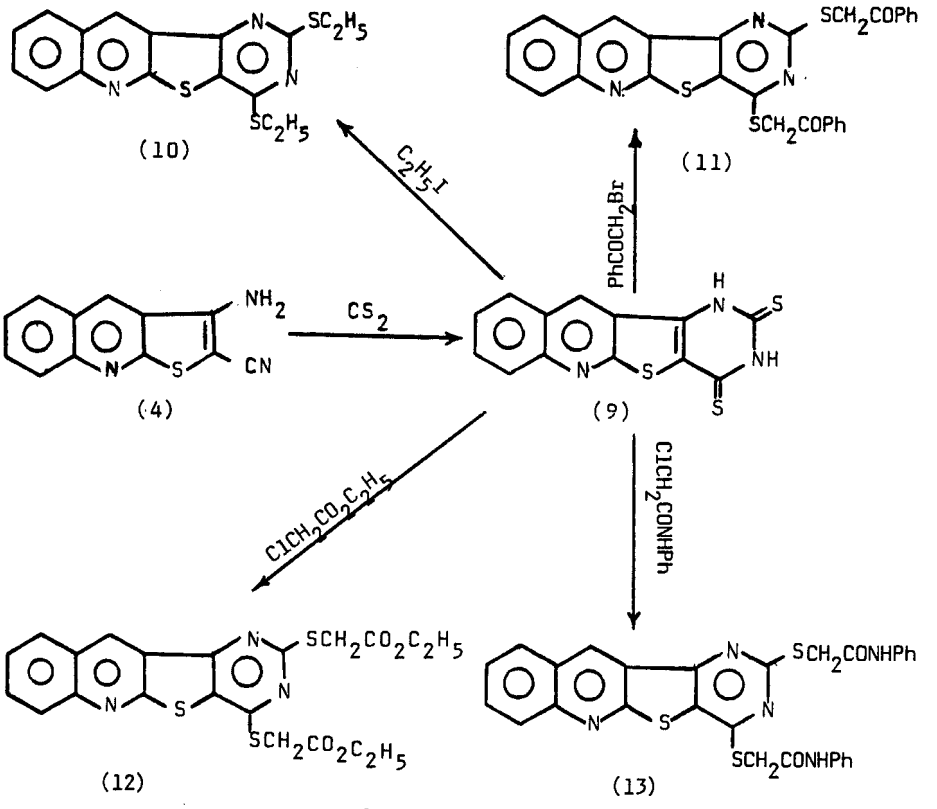
b]quinolin-2-carboxamide (**8**) which was also obtained *via* direct interaction of **1** with chloroacetamide in the presence of ethoxide. On the other hand, reaction of **1** with ethyl chloroacetate in the presence of an equal molar ratio of sodium acetate or triethylamine gave ester **6**. Compound **6** upon warming in sodium ethoxide solution or refluxing in ethanol containing excess amounts of sodium acetate, readily cyclized into ethyl 3-amino-thieno[2,3-b]quinoline-2-carboxylate (**5**) (Scheme I).

Interaction of **4** with carbon disulfide in heated pyridine yielded 1,2,3,4-tetrahydro-2,4-dithioxopyrimido[4′,5′:4,5]-thieno[2,3-b]quinoline (**9**).[12] Reaction of **9** with some halo-compounds namely ethyl iodide, phenacyl bromide, ethyl chloroacetate and chloroacetanilide gave 2,4-di(substituted thio)-pyrimido[4′,5′:4,5]thieno[2,3-b]quinolines (**10**, **11**, **12** and **13**, respectively) (Scheme II).

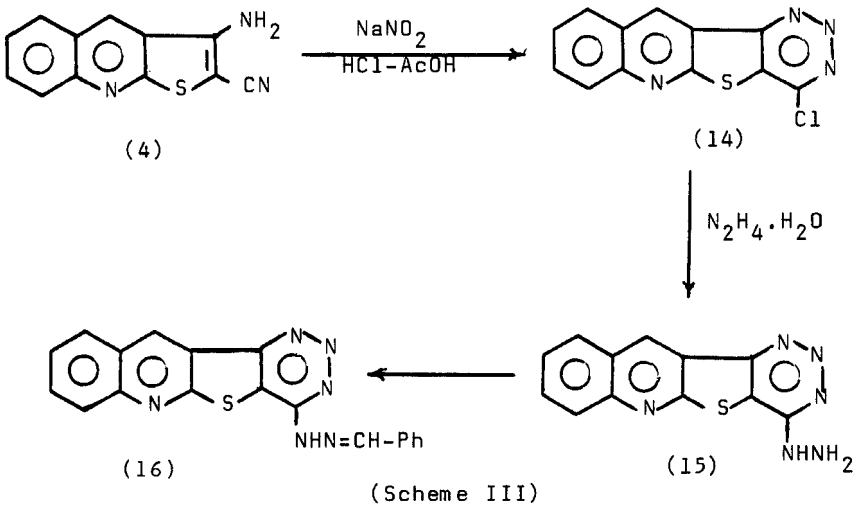
Also, treatment of **4** in HCl-AcOH mixture with sodium nitrite solution at low temperature gave 4-chloro-1,2,3-triazino-[4′,5′:4,5]thieno[2,3-b]quinoline (**14**) which, in turn, was reacted with hydrazine hydrate to yield the corresponding hydrazino-compound **15**. Condensation of **15** with benzaldehyde gave hydrazone **16** (Scheme III).



Scheme I

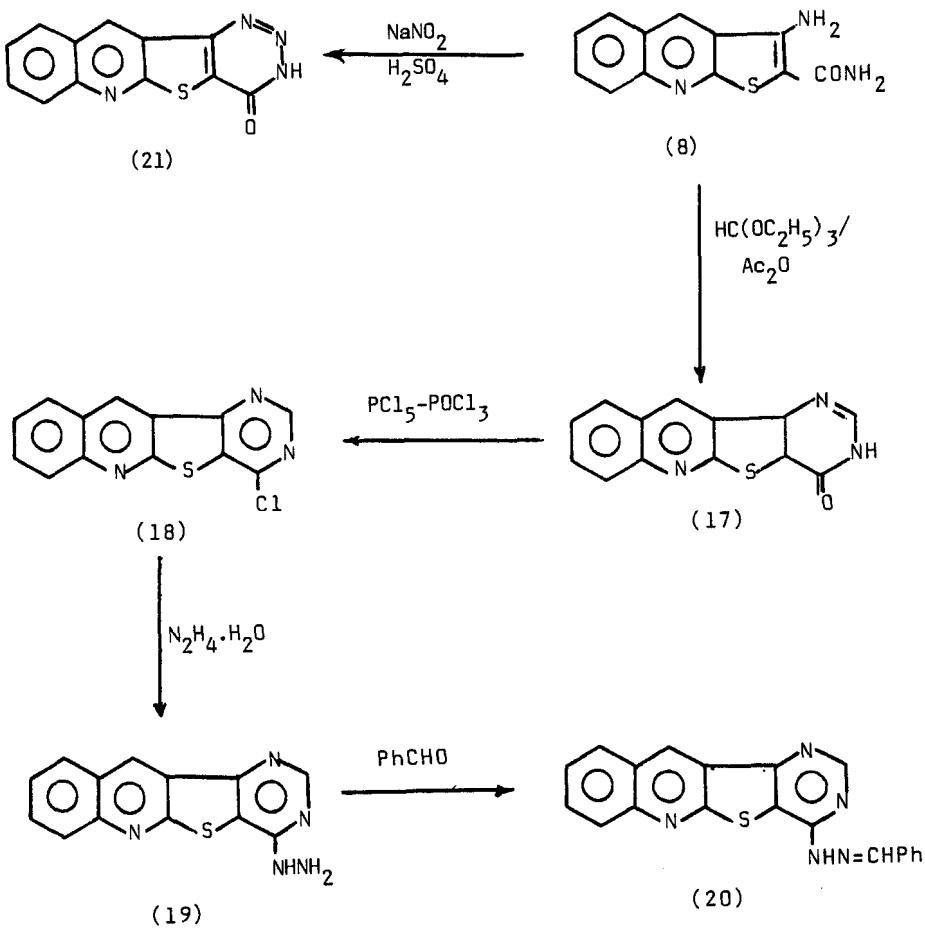


Scheme II



(Scheme III)

Condensation of 3-amino-thieno[2,3-b]quinoline-2-carboxamide (**8**) with triethyl orthoformate in refluxing acetic anhydride led to pyrimidine derivative **17**. On heating of **17** with PCl_5-$POCl_3$ mixture at refluxing temperature, 4-chloro-pyrimido[4′,5′:4,5]thieno[2,3-b]quinoline (**18**) was obtained. Reaction of **18** with hy-



Scheme IV

drazine hydrate yielded hydrazino-compound **19** which was condensed with benzaldehyde giving hydrazone **20**. Also, treatment of **8** with nitrous acid furnished triazinone derivative **21** (Scheme IV).

The structure of the synthesized compounds were confirmed on the basis of their elemental analyses (Experimental part), IR and ^{1}H-NMR spectra (Table I).

Biological Activity

Most of the synthesized compounds were tested *in vitro* as antibacterials against eight Gram-negative and Gram-positive organisms by usual paper disc diffusion method.[13] Thus, sterilized 5 mm paper disc immersed in drug solution (20 mg in 1 ml of N,N-dimethylformamide) was placed in a Petri dish containing 25–30 ml of nutrient agar inoculated with 18–24 h test culture. Incubation was carried out at 37°C for 36 h and zones of inhibition were measured in mm. Among the compounds tested, only **3**, **9**, **10**, **12**, **13**, **14** and **18** exhibited antibacterial activities of high order. The rest of the compounds showed either moderate or no activity

TABLE I

IR and ^{1}H-NMR data for newly synthesized compounds

Compd. No.	IR (Selected bands)	^{1}H-NMR
2	2220 (C≡N)	($CDCl_3$);8.25(s,1H,CH-quinoline at C-4); 7.30-8.00 (m,4H, Ar-H); 3.20-3.50 (q,2H, SCH_2) and 1.30-1.60 (t, 3H, CH_3).
3	3420, 3340(NH_2) and 1640 (C=O).	(CF_3CO_2D); 9.35(s,1H, CH-quinoline at C-4); 7.65-8.30 (m,4H, Ar-H) and 2.50 (s,3H, $COCH_3$).
4	3400, 3340(NH_2) and 2200 (C≡N)	-----
5	3420,3280(NH_2) and 1660(C=O)	-----
6	2220(C=N) and 1725 (C=O)	($CDCl_3$);8.30(s,1H,CH-quinoline at C-4); 7.35-7.80 (m,4H,Ar-H); 4.10-4.35(m,4H;SCH_2 and OCH_2) and 1.20-1.45 (t,3H,CH_3).
7	3380,3200(NH_2); 2220(C=N) and 1660(C=O).	------
8	3430,3360,3270, 3140(NH_2) and 1650(C=O)	(CD_3SOCD_3);9.00(s,1H,CH-quinoline at C-4);7.50-8.10 (m,4H,Ar-H);7.20(s,2H,NH_2) and 7.35 (s,2H,NH_2).
9	3355(NH) and 1220(C=S).	-------
10	1600(C=N)	($CDCl_3$);8.90(s,1H,CH-quinoline at C-11);7.40-8.10 (m,4H,Ar-H);3.20-3.60 (m,4H, 2XSCH_2) and 1.40-1.70 (m,6H,2XCH_3).
11	1680(C=O)	($CDCl_3$);8.80(s,1H,CH-quinoline at C-11);7.25-8.30 (m,14H, Ar-H); 4.75 (s,2H,SCH_2) and 4.55 (s,2H , SCH_2).
12	1725(C=O,ester)	($CDCl_3$);8.80(s,1H,CH-quinoline at C-11);7.30-8.10 (m,4H, Ar-H); 3.80-4.40(m,8H, 2XSCH_2 and 2XOCH_2 and 1.10-1.50(m,6H,2XCH_3).
13	3280(NH) and 1660(C=O)	------
14	1590(C=N)	($CDCl_3$);8.90(s,1H,CH-quinoline at C-11); 7.30-8.10 (m,4H,Ar-H).
15	3300,3190($NHNH_2$) and 1640(C=O).	---

TABLE I (*Continued*)

Compd. No.	IR (Selected bands)	^{1}H-NMR
16	3190(NH) and 1610 (C=N)	(CF_3CO_2D);9.80(s,1H,CH-quinoline at C-11) and 7.30-8.40(m,10H: 9H,Ar-H and 1H of -N=CH-group).
17	3200-2400(NH) and 1650(C=O)	---
18	1600(C=N)	(CF_3CO_2D); 9.60(s,1H,CH-quinoline at C-11); 9.30(s,1H,CH-pyrimidine) and 7.80-8.40 (m,4H,Ar-H).
19	3300,3200($NHNH_2$) and 1630 (C=N)	---
20	3210 (NH) and 1600 (C=N)	(CF_3CO_2D);9.80(s,1H,CH-quinoline at C-11); 9.00(s,1H,CH-pyrimidine) and 7.50-8.60(m, 10H; 9H, Ar-H and 1H of -N=CH-group).
21	3200-2400(NH) and 1650(C=O).	---

(Table II). The antibacterial activities varied with the species but the difference was marginal.

EXPERIMENTAL

All melting points are uncorrected. The IR spectra were run on a Pye-Unicam SP 3-100 spectrophotometer using KBr disc technique (wave numbers in cm^{-1}). The ^{1}H NMR spectra were recorded on a Varian EM-390 90 MHz ^{1}H NMR spectrometer using TMS as internal standard; chemical shifts are given in ppm (δ-scale).

Reaction of compound **1** *with ethyl iodide, chloroacetone, chloroacetonitrile, ethyl chloroacetate and chloroacetamide; formation of compounds* **2**, **3**, **4**, **5** *and* **7**, *respectively. General Procedure:* A mixture of **1** (1.86 g, 0.01 mole), respective halocompound (0.011 mole) and fused sodium acetate (4.1 g, 0.05 mole) in abs. ethanol was refluxed for 5 hrs. The formed solid was collected by filtration, washed several times with ethanol and finally with water and recrystallized from suitable solvent. In this way the following compounds were prepared:

a) *3-Cyano-2-ethylthioquinoline* (**2**): Obtained from **1** and ethyl iodide. It recrystallized from dil. alcohol as colorless needles, m.p. 110–111°C, yield 2.0 g (94%).

Anal. Calcd. for $C_{12}H_{10}N_2S$: C, 67.26; H, 4.70; N, 13.07; S, 14.96%. Found: C, 66.97; H, 4.94; N, 13.15; S, 15.00%.

b) *2-Acetyl-3-amino-thieno[2,3-b]quinoline* (**3**): Obtained from **1** and chloroacetone. It recrystallized from $CHCl_3$-EtOH mixture as scarlet red needles, m.p. 260–263°C, yield 2.2 g (91%).

Anal. Calcd. for $C_{13}H_{10}N_2OS$: C, 64.44; H, 4.16; N, 11.56; S, 13.23%. Found: C, 64.13; H, 4.17; N, 11.91; S, 13.00%.

c) *3-Amino-2-cyano-thieno[2,3-b]quinoline* (**4**): Obtained from **1** and chloroacetonitrile. It recrystallized from $CHCl_3$-EtOH mixture as yellow needles, m.p. 285–290°C, yield 2.2 g (98%).

Anal. Calcd. for $C_{12}H_7N_3S$: C, 63.98; H, 3.13; N, 18.65; S, 14.23%. Found: C, 64.07; H, 3.17; N, 18.39; S, 14.40%.

TABLE II

Biological activities (inhibition zones in mm)

Compd.	E. coli	Prot. vulgaris	Pseud. aeruginosa	Se. rhodnii	B. cereus	St. citreus	M. luteus	M. roseus
3	8	-ve	7	6	9	10	6	7
4	6	-ve	-ve	6	7	6	7	6
6	9	8	7	6	-ve	-ve	-ve	-ve
7	6	7	-ve	-ve	6	-ve	-ve	6
8	8	6	6	-ve	6	-ve	-ve	6
9	13	6	-ve	-ve	12	13	6	7
10	16	8	-ve	7	10	9	10	9
11	-ve	-ve	-ve	6	9	-ve	-ve	-ve
12	9	8	9	7	-ve	-ve	7	6
13	14	8	6	6	7	7	7	9
14	7	7	7	-ve	14	-ve	9	7
15	10	7	7	9	9	9	13	9
16	6	6	6	6	-ve	-ve	-ve	-ve
17	8	-ve	6	6	8	-ve	-ve	-ve
18	6	7	6	8	9	6	6	6
19	10	7	7	-ve	-ve	-ve	-ve	6
20	-ve	8	6	-ve	6	-ve	-ve	-ve

-ve : Compound not active .

d) *Ethyl 3-amino-thieno[2,3-b]quinoline-2-carboxylate* (**5**): Obtained from **1** and ethyl chloroacetate. It recrystallized from ethanol as red needle crystals, m.p. 272–3°C, yield 2.0 g (73%).

Anal. Calcd. for $C_{14}H_{12}N_2O_2S$: C, 61.75; H, 4.44; N, 10.29; S, 11.77%. Found: C, 61.65; H, 4.32; N, 10.51; S, 11.90%.

e) *(3-Cyano-2-quinolinylthio)acetamide* (**7**): Obtained from **1** and chloroacetamide. It recrystallized from ethanol as pale yellow needles, m.p. 238–240°C, yield 2.0 g (82%).

Anal. Calcd. for $C_{12}H_9N_3OS$: C, 59.24; H, 3.79, N, 17.26, S, 13.18%. Found: C, 59.37; H, 3.80; N, 17.01; S, 13.00%.

Synthesis of ethyl (3-cyano-2-quinolinylthio)acetate (**6**): To a suspension of **1** (1.86 g, 0.01 mole) and ethyl chloroacetate (1.23 g, 0.01 mole) in ethanol (15 ml), 0.01 mole of sodium acetate (0.82 g) or triethyl amine (1.0 g) was added. The contents were refluxed for one hour and allowed to cool. The precipitate was collected and recrystallized from ethanol as pale yellow needles, m.p. 114°C, yield 2.3 g (85%).

Anal. Calcd. for $C_{14}H_{12}N_2O_2S$: C, 61.75; H, 4.44; N, 10.29; S, 11.77%. Found: C, 61.90; H, 4.29; N, 10.63; S, 12.00%.

Cyclization of compound **6**; *formation of* **5**: Compound **6** (1.36 g, 0.05 mole) was dissolved in sodium ethoxide solution (10 mg sodium in 50 ml ethanol) and refluxed for 5 mins. The product obtained was identified as ethyl 3-amino-thieno[2,3-b]quinoline-2-carboxylate (**5**): m.p. 272–3°C; yield 1.25 g (92%). Also, refluxing of **6** (1.36 g, 0.005 mole) in ethanol containing sodium acetate (1.64 g, 0.02 mole) for 4 hrs yielded thienoquinoline **5** in 73% yield (1.0 g).

Synthesis of 3-amino-thieno[2,3-b]quinoline-2-carboxamide (**8**):

Method A: 0.01 Mole of compound **7** (2.43 g) was suspended in sodium ethoxide solution (10 mg sodium in 50 ml ethanol) and refluxed for 15 min. The solid formed was collected and recrystallized from ethanol in the form of golden yellow fine needles of **8**, m.p. 260°C (dec.), yield 3.0 g (92%).

Anal. Calcd. for $C_{12}H_9N_2OS$: C, 59.24; H, 3.79; N, 17.26; S, 13.18%. Found: C, 59.60; H, 3.77; N, 17.20; S, 13.40%.

Method B: A mixture of compound **1** (1.86 g, 0.01 mole) and chloroacetamide (0.94 g, 0.01 mole) in sodium ethoxide solution (0.46 g sodium in 50 ml ethanol) was refluxed for ½ hr. The product formed upon recrystallization was identical to that described in method A.

Synthesis of 1,2,3,4-tetrahydro-2,4-dithioxopyrimido[4',5':4,5]thieno[2,3-b]quinoline (**9**): To a solution of **4** (2.0 g) in dry pyridine (40 ml), carbon disulfide (10 ml) was added. The contents were heated on a water bath for 10 hrs. The solvents were removed in vacuum and the residue was washed with water and crystallized from DMF-EtOH to give **9** as red needles, m.p. >300°C, yield 1.86 g (70%).

Anal. Calcd. for $C_{13}H_7N_3S_3$: C, 51.81; H, 2.34; N, 13.94; S, 31.91%. Found: C, 51.75; H, 2.31; N, 13.90; S, 31.50%.

Reaction of compound **9** *with some halocompounds. General procedure:* A mixture of **9** (0.3 g, 0.001 mole) sodium acetate (0.25 g, 0.003 mole) and halocompound (0.0022 mole) in ethanol (20 ml) was refluxed for 2 hrs. On cooling, the product thus formed was collected and recrystallized from the suitable solvent. In this way the following compounds (**10–13**) were prepared:

a) *2,4-Di(ethylthio)-pyrimido[4',5':4,5]thieno[2,3-b]quinoline* (**10**): It was prepared by using ethyl iodide and recrystallized from ethanol as pale yellow needles, m.p. 161–2°C, yield 0.3 g (84%).

Anal. Calcd. for $C_{17}H_{15}N_3S_3$: C, 57.11; H, 4.23; N, 11.75; S, 26.90%. Found: C, 57.33; H, 4.20; N, 11.90; S, 27.10%.

b) *2,4-Di(phenacylthio)-pyrimido[4',5':4,5]thieno[2,3-b]quinoline* (**11**): It was prepared by using phenacyl bromide and recrystallized from $CHCl_3$-EtOH mixture to give **11** as red prisms, m.p. 209–211°C, yield 0.45 g (84%).

Anal. Calcd. for $C_{29}H_{19}N_3O_2S_3$: C, 64.78; H, 3.56; N, 7.82; S, 17.89%. Found: C, 64.88; H, 3.49; N, 7.70; S, 17.65%.

c) *2,4-Di(ethoxycarbonylmethylthio)-pyrimido[4',5'-4,5]thieno[2,3-b]quinoline* (**12**): It was prepared by using ethyl chloroacetate and recrystallized from ethanol as pale yellow needles, m.p. 152–3°C, yield 4.2 g (88%).

Anal. Calcd. for $C_{21}H_{19}N_3O_4S_3$: C, 53.26; H, 4.04; N, 8.87; S, 20.31%. Found: C, 53.00; H, 4.10; N, 8.79; S, 20.00%.

d) *2,4-Di(N-phenylcarboxamidomethylthio)-pyrimido[4',5':4,5]thieno[2,3-b]quinoline* (**13**): It was prepared by using chloroacetanilide and recrystallized from $CHCl_3$-EtOH mixture as pale yellow needles, m.p. 293–6°C, yield 0.46 g (81%).

Anal. Calcd. for $C_{29}H_{21}N_5O_2S_3$: C, 61.36; H, 3.73; N, 12.34; S, 16.94%. Found: C, 61.35; H, 3.71; N, 12.71; S, 17.30%.

Synthesis of 4-chloro-1,2,3-triazino[4',5'-4,5]thieno[2,3-b]quinoline (**14**): To a cold solution of **4** (2.5 g, 0.011 mole) in 30 ml of acetic acid and 15 ml of concentrated hydrochloric acid, was added a solution of 0.95 g (0.014 mole) of sodium nitrite in 10 ml of water. After completion of addition the ice bath was removed and stirring continued for 2 more hours. The product was crystallized from $CHCl_3$-EtOH mixture as red needles of **14**, m.p. 247–9°C, yield 1.7 g (57%).

Anal. Calcd. for $C_{12}H_5ClN_4S$: C, 52.85; H, 1.85; N, 20.54; S, 11.76; Cl, 13.00%. Found: C, 52.55; H, 1.87; N, 20.43; S, 11.70; Cl, 13.20%.

Synthesis of 3,4-dihydro-4-oxopyrimido[4',5':4,5]thieno[2,3-b]quinoline (**17**): Triethyl orthoformate (1 g, 0.0067 mole) and compound **8** (1.38 g, 0.0057 mole) in redistilled acetic anhydride (30 ml) were heated at 120°C for one hour. The reaction mixture was cooled, the formed precipitate was collected and recrystallized from dioxane as white crystals of **17**, m.p. >300, yield 1.2 g (83%).

Anal. Calcd. for $C_{13}H_7N_3OS$: C, 61.65; H, 2.79; N, 16.59; S, 6.32%. Found: C, 62.03; H, 2.68; N, 16.49; S, 6.30%.

Synthesis of 4-chloropyrimido[4',5'-4,5]thieno[2,3-b]quinoline (**18**): Compound **17** (2 g) in an excess amount of $POCl_3$–PCl_5 (25 ml + 5 gm) was refluxed for 4 hrs. The cooled reaction mixture was poured with stirring into ice-cold water. The solid thus separated was crystallized from ethanol as white needles, m.p. 255–7°C, yield 1.3 g (60%).

Anal. Calcd. for $C_{13}H_6ClN_3S$: C, 57.46; H, 2.23; N, 15.46; S, 11.80; Cl, 13.05%. Found: C, 57.54; H, 2.34; N, 15.41; S, 11.65; Cl, 13.50%.

Reaction of **14** *and* **18** *with hydrazine hydrate; formation of* **15** *and* **19**, *respectively.* A mixture of chloro-compound (**14** or **18**) (0.01 mole) and hydrazine hydrate 99% (1 ml, 0.02 mole) in ethanol (50 ml) was refluxed for 2 hrs. The product thus precipitated was collected and recrystallized from dioxane as pale yellow crystals.

The following compounds were prepared as in the above general procedure:

a) *4-Hydrazion-1,2,3-triazino[4',5':4,5]thieno[2,3-b]quinoline* (**15**): Obtained from compound **14** in 90% yield, m.p. 275°C (dec.).

Anal. Calcd. for $C_{12}H_8N_6S$: C, 53.72; H, 3.01; N, 31.32; S, 11.95%. Found: C, 53.62; H, 3.05; N, 31.61; S, 12.35%.

b) *4-Hydrazino-pyrimido[4',5':4,5]thieno[2,3-b]quinoline* (**19**): Obtained from **18** in 92% yield, m.p. > 300°C.

Anal. Calcd. from $C_{13}H_9N_5S$: C, 58.41; H, 3.39; N, 26.20; S, 11.99%. Found: C, 58.75; H, 3.36; N, 26.50; S, 11.78%.

Condensation of **15** *and* **19** *with benzaldehyde; formation of* **16** *and* **20**, *respectively:* A mixture of hydrazino-compound (**15** or **19**) (0.005 mole) and benzaldehyde (0.53 g, 0.005 mole) in dioxane (30 ml) was refluxed for 3 hrs. The solid product thus precipitated after cooling was collected and recrystallized from dioxane as yellow needles of **16** and/or **20**. In this way the following compounds were prepared:

a) *Benzaldehyde, (1,2,3,-triazino[4',5':4,5]thieno[2,3-b]quinolin-4-yl)hydrazone* (**16**): Obtained from **15** in 95% yield; m.p. 293–5 (dec.).

Anal. Calcd. for $C_{19}H_{12}N_6S$: C, 64.03; H, 3.39; N, 23.58; S, 9.00%. Found: C, 64.00; H, 3.41; N, 23.90; S, 9.35%.

b) *Benzaldehyde, (pyrimido[4',5':4,5]thieno[2,3-b]quinolin-4-yl)-hydrazone* (**20**): Obtained from **19** in 90% yield; m.p. > 300°C.

Anal. Calcd. for $C_{20}H_{13}N_5S$: C, 67.59; H, 3.69; N, 19.70; S, 9.02%. Found: C, 67.70; H, 3.62; N, 19.53; S, 9.40%.

Synthesis of 1,2,3-triazino[4',5':4,5]thieno[2,3-b]quinoline (**21**). To a cold solution of **8** (1.36 g, 0.0056 mole) in concentrated sulphuric acid (10 ml) and glacial acetic acid (20 ml), 0.5 g (0.007 mole) sodium nitrite dissolved in 10 ml water was added dropwise with constant stirring during 10 minutes. The mixture was stirred in the cold for one additional hour and diluted with water. The precipitate thus formed was collected and crystallized from DMF as white crystals, m.p. >300°C, yield 1.2 g (85%).

Anal. Calcd. for $C_{12}H_6N_4OS$: C, 56.69, H, 2.38; N, 22.04; S, 12.61%. Found: C, 56.83, H, 2.40, N, 22.12; S, 12.50%.

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