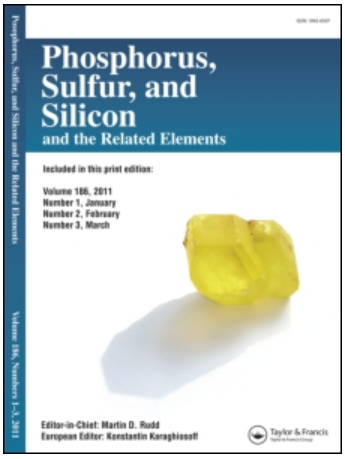

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SYNTHESIS OF THIENOQUINOLINES: PART I. SYNTHESIS OF NOVEL HETEROCYCLO-THIENO[2,3-b]QUINOLINE DERIVATIVES

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SYNTHESIS OF THIENOQUINOLINES: PART I. SYNTHESIS OF NOVEL HETEROCYCLO-THIENO[2,3-b]QUINOLINE DERIVATIVES

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Ethyl 3-amino-4-(*p*-chlorophenyl)-5,6,7,8-tetrahydrothieno[2,3-b]quinoline-2-carboxylate (**II$_a$**) was hydrolysed to the sodium salt of the corresponding acid (**III**) which upon treatment with acetic anhydride furnished the oxazinone derivative **IV**. Recyclization of **IV** with ammonium acetate, hydrazine hydrate and/or aniline afforded the pyrimidine derivatives **V**, **VIII** and **X** respectively. Alkylation of **V** gave the *N*-alkylated products **VI** and **VII**. Compound **VIII** condensed with *p*-nitrobenzaldehyde to give the Schiff base **IX**. On the other hand, condensation of 3-amino-4-(*p*-chlorophenyl)-5,6,7,8-tetrahydro-thieno-[2,3-b]quinoline-2-carbonitrile (**II$_b$**) with triethyl ortho-formate gave methanimidate derivative **XI** which reacted with hydrazine hydrate to yield **XII**. Treatment of **XII** with formic acid gave *s*-triazolo compound **XIII**. 3-Amino-4-(*p*-chlorophenyl)-5,6,7,8-tetrahydro-thieno[2,3-b]quinoline-2-carboxamide (**II$_c$**) was also reacted with phenyl isothiocyanate, phenyl isocyanate, carbon disulfide and/or nitrous acid to afford the desired compounds **XVII**, **XIX**, **XXI** and **XXIII** respectively. Alkylation of **XVII**, **XXI** and **XXIII** gave **XVIII**, **XXII** and **XXIV–XXVI**. Furthermore, the reaction products of **II$_b$** and **II$_c$** with acetic anhydride were identified.

Key words: Tetrahydroquinoline; thienoquinoline; thienoquinolinopyrimidine; thienoquinolinotriazine.

INTRODUCTION

Some quinolines are reported to possess antimalarial, antifilarial and antihypertensive activities.[1–4] Also, the biological activity of many heterocyclic compounds containing a thiophene ring has been reviewed.[5,6] On the other hand, the survey of the literature revealed that only few thieno[2,3-b]quinolines are known.[7–10] In view of these observations and as a continuation of our previous work on thieno[2,3-b]quinolines,[11–13] we undertook the synthesis of some new heterocyclic compounds containing the thieno[2,3-b]quinoline moiety fused with a pyrimidine or a triazine nucleus with the hope that they may be biologically active compounds.

RESULTS AND DISCUSSION

Our approach to the synthesis of the desired compounds started from 3-amino-4-(*p*-chlorophenyl)-2-substituted-5,6,7,8-tetrahydrothieno[2,3-b]quinolines (**II$_{a-c}$**) which were prepared according to the literature method[10] as follows:

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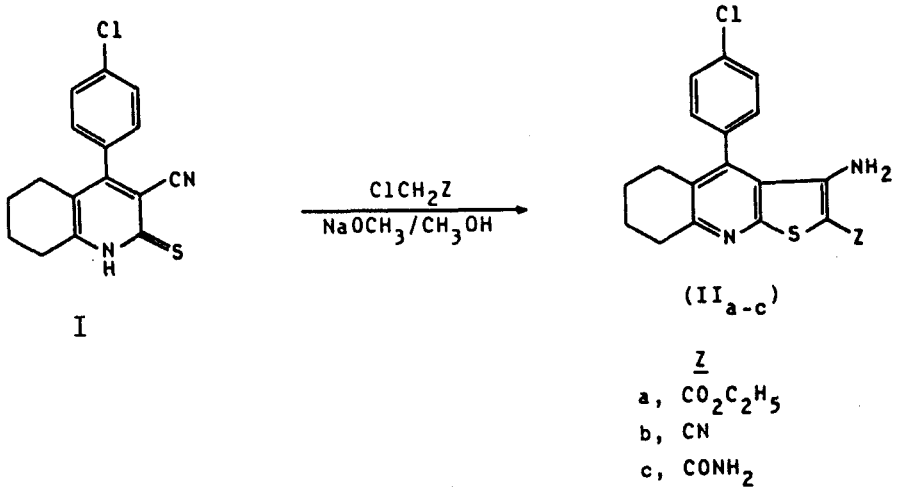
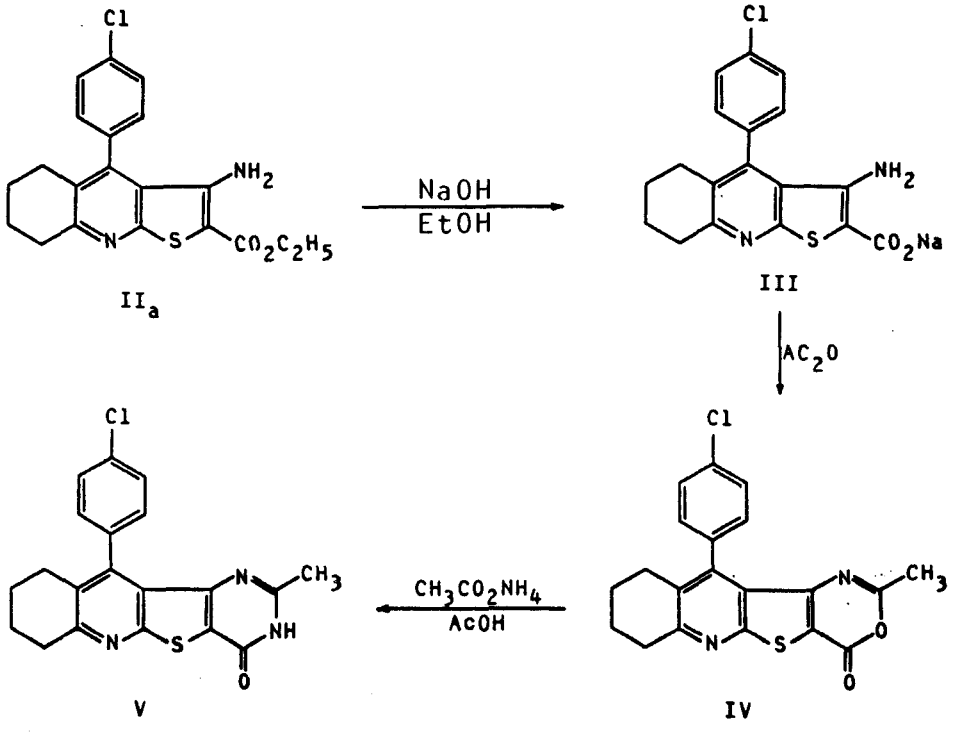
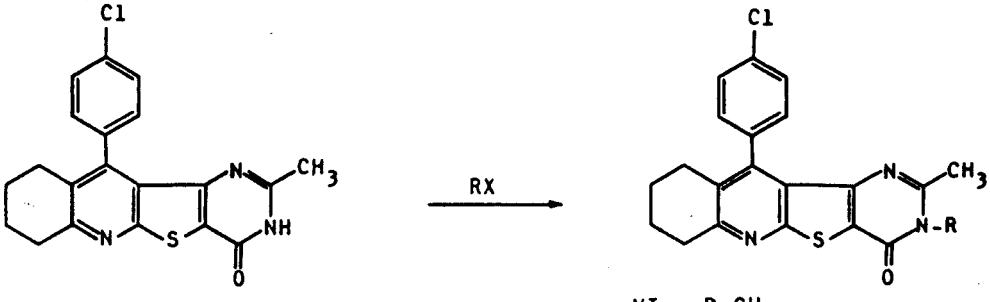


Ethyl 3-amino-4-(*p*-chlorophenyl)-5,6,7,8-tetrahydro-thieno[2,3-b]-quinoline-2-carboxylate (**II**$_a$) was hydrolysed by refluxing in ethanolic sodium hydroxide solution to the sodium salt of the corresponding acid (**III**) which on treatment with acetic anhydride gave 2-methyl-11-(*p*-chlorophenyl)-7,8,9,10-tetrahydroquinolino[3′,2′:4,5]thieno[3,2-d]oxazin-4-one (**IV**).



Interaction of oxazinone IV with ammonium acetate in acetic acid furnished 2-methyl-11-(*p*-chlorophenyl-7,8,9,10-tetrahydroquinolino-[3′,2′:4,5]thieno[3,2-d]-pyrimidin-4(3H)-one (**V**) which, in turn, underwent *N*-alkylation when treated with

methyl iodide and/or ethyl chloroacetate in DMF containing potassium carbonate to yield the pyrimidinone derivatives **VI** and **VII** respectively.

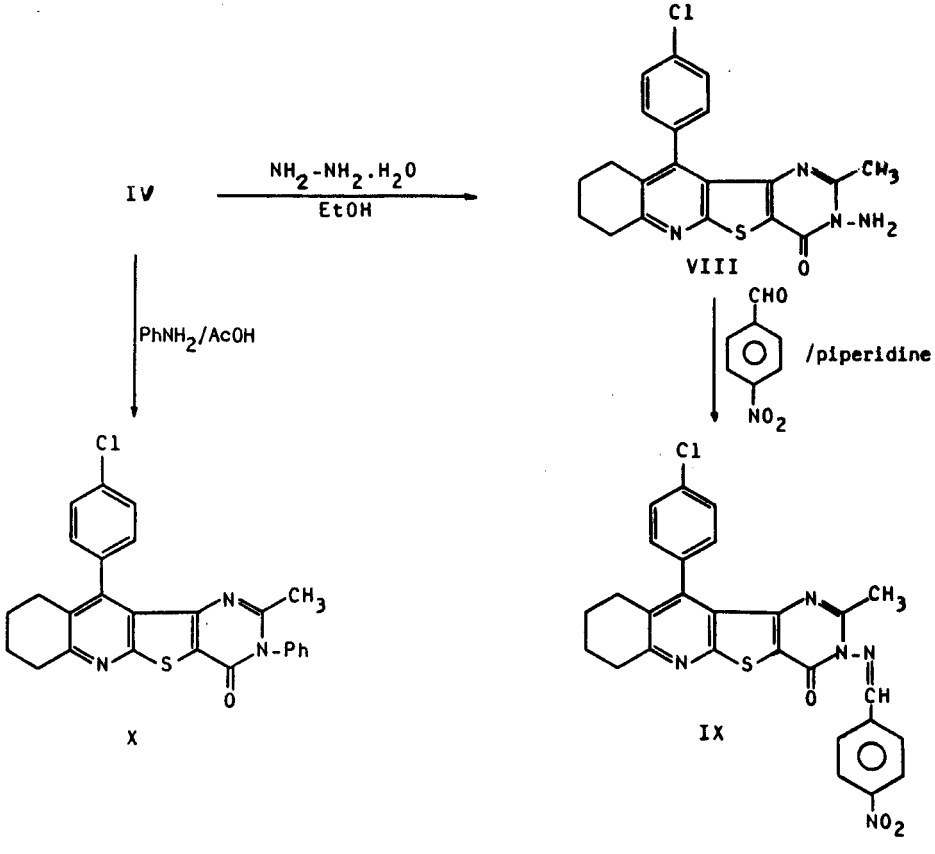


V

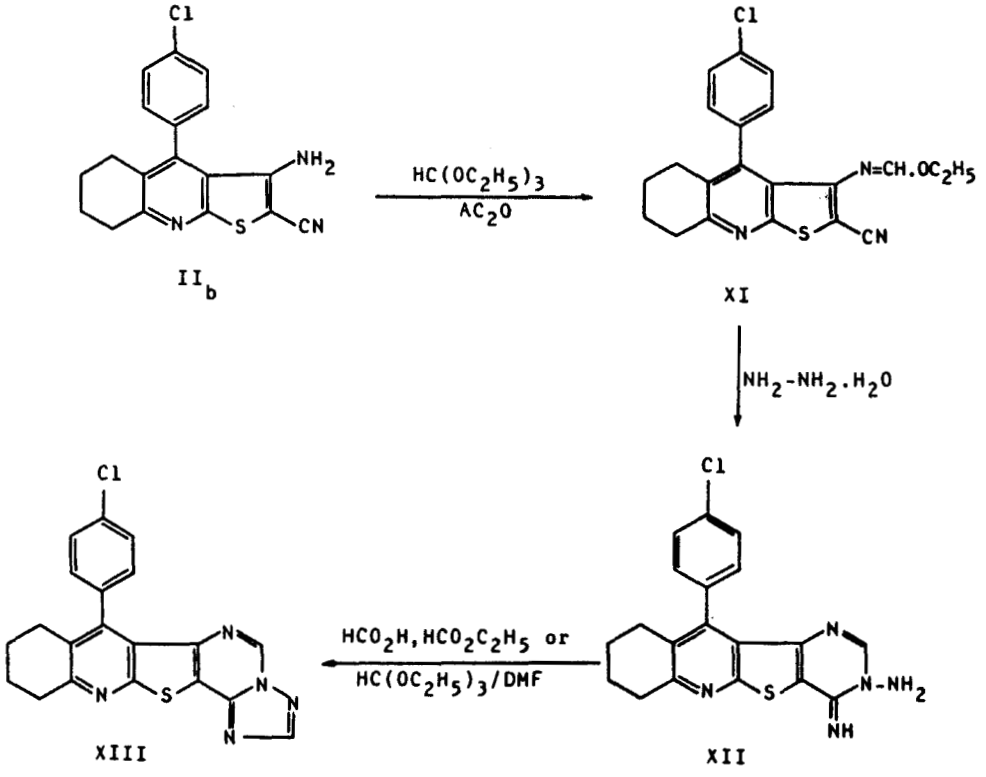
VI , R=CH_3

VII , R=$CH_2CO_2C_2H_5$

Similarly, reaction of oxazinone **IV** with hydrazine hydrate in refluxing ethanol gave 3-amino-2-methyl-11-(*p*-chlorophenyl)-7,8,9,10-tetrahydroquinolino[3′,2′:-4,5]thieno[3,2-d]pyrimidin-4(3H)-one (**VIII**). Condensation of **VIII** with *p*-nitrobenzaldehyde in refluxing ethanol and a few drops of piperidine yielded the corresponding Schiff base **IX**. Also, oxazinone derivative **IV** underwent ring transformation into the pyrimidinone derivative **X** upon heating with aniline in acetic acid.

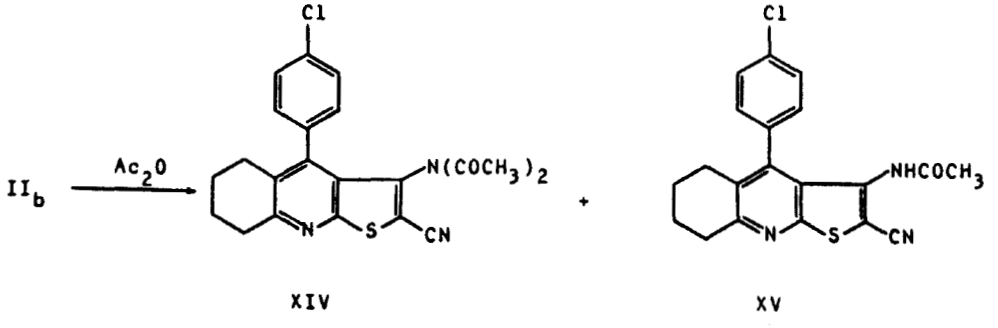


On the other hand, condensation of $\mathbf{II_b}$ with triethyl orthoformate in refluxing acetic anhydride led to the formation of ethyl *N*-(2-cyano-4-*p*-chlorophenyl-5,6,7,8-tetrahydro-thieno[2,3-b]quinolin-3-yl)-methanimidate (**XI**) in high yield. Treatment of **XI** with hydrazine hydrate gave 4-imino-11-(*p*-chlorophenyl)-7,8,9,10-tetrahydroquinolino[3′,2′:4,5]-thieno[3,2-d]pyrimidin-3(4H)-amine (**XII**) which condensed with formic acid, ethyl formate or with triethyl orthoformate in DMF to afford the *s*-triazolo derivative (**XIII**).

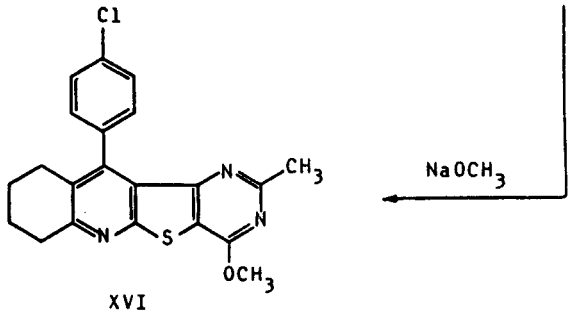


$\mathbf{II_b}$ XI XIII XII

Refluxing of $\mathbf{II_b}$ in acetic anhydride gave a mixture of diacetyl and monoacetyl derivatives (**XIV** and **XV** respectively) which could be isolated by fractional crystallization. Compound **XV** upon treatment with sodium methoxide in methanol was cyclized into 2-methyl-4-methoxy-11-(*p*-chlorophenyl)-7,8,9,10-tetrahydroquinolino[3′,2′:4,5]-thieno[3,2-d]pyrimidine (**XVI**).[14]

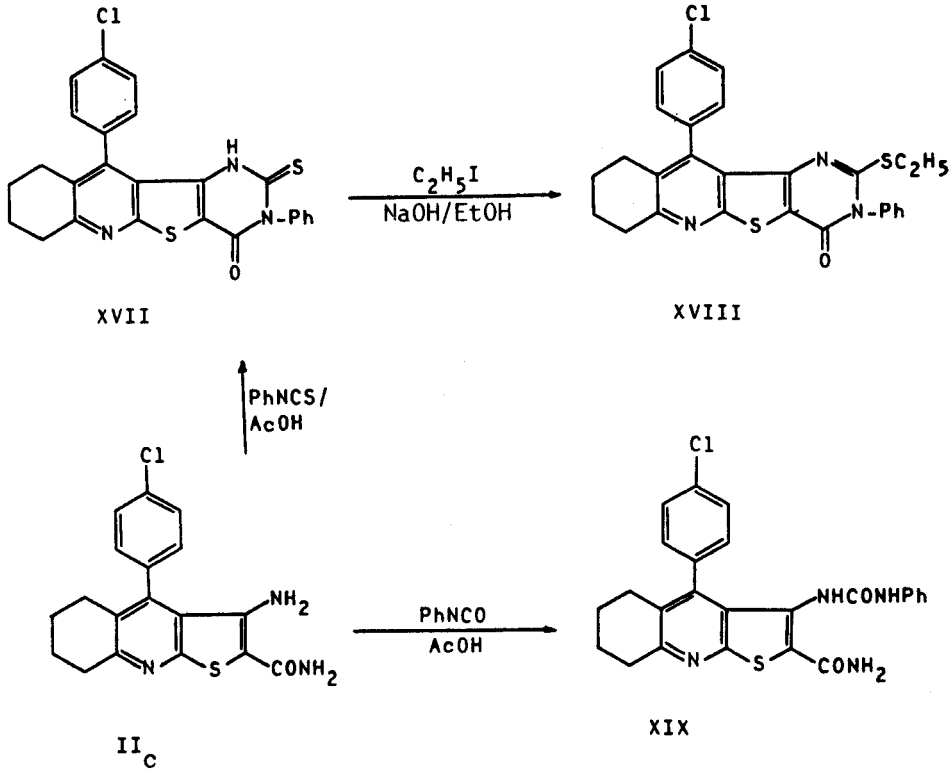


XIV XV



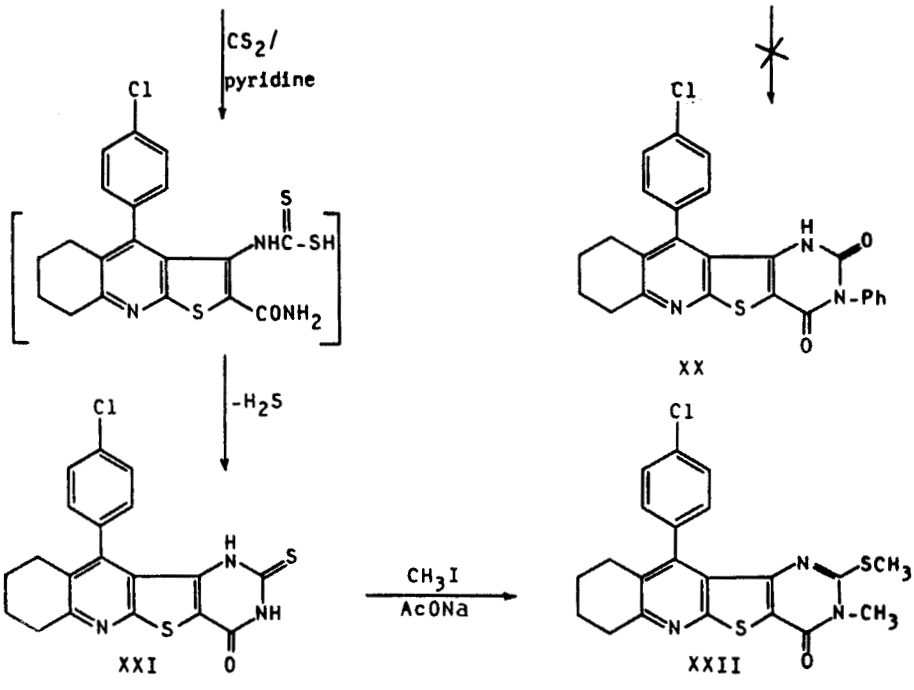
XVI

Moreover, reaction of $\mathbf{II}_c$ with phenyl isothiocyanate in acetic acid gave 11-(*p*-chlorophenyl)-3-phenyl-2-thioxo-7,8,9,10 - tetrahydroquinolino - [3′,2′:4,5] thieno-[3,2-d]pyrimidin-4(1H, 3H)-one (**XVII**) which was ethylated easily in ethanolic sodium hydroxide to give the corresponding 2-ethylthio compound (**XVIII**). In contrast, reaction of $\mathbf{II}_c$ with phenyl isocyanate gave urea derivative **XIX**. Attempts to cyclize **XIX** into pyrimidinedione derivative **XX** by heating in pyridine or DMF were unsuccessful. Similarly, interaction of $\mathbf{II}_c$ with carbon disulfide in pyridine yielded compound **XXI** which reacted with an excess amount of methyl iodide, in the presence of sodium acetate, to give 3-methyl-2-methylthio-11-(*p*-chlorophenyl)-7,8,9,10-tetrahydroquinolino[3′,2′:4,5]thieno[3,2-d]-pyrimidin-4(3H)-one (**XXII**).

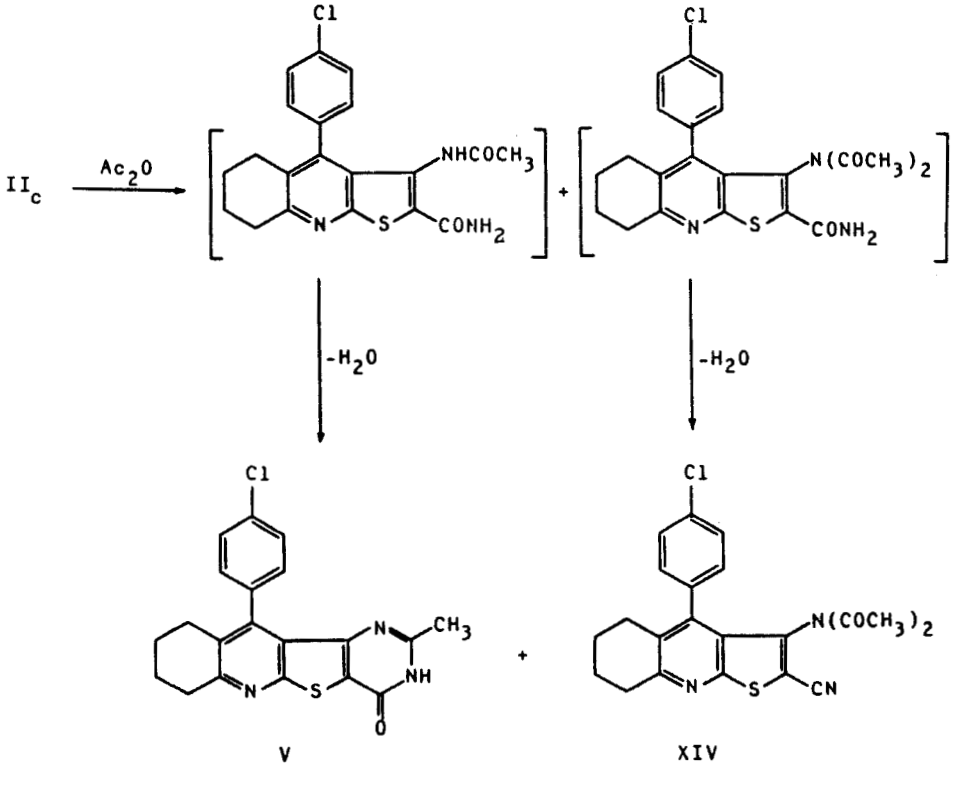


XVII XVIII

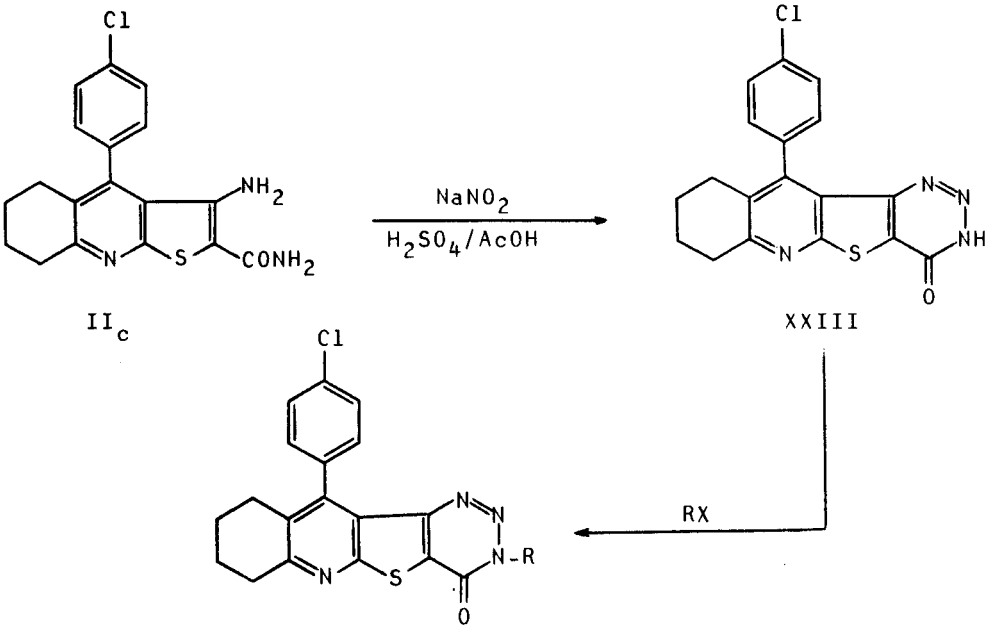
$\mathbf{II}_c$ XIX



Furthermore, refluxing of $\mathbf{II}_c$ in acetic anhydride yielded a mixture of **V** and **XIV** which were also prepared from **IV** and $\mathbf{II}_b$ as described above. The reaction pathway can be illustrated as:



Finally, diazotization of $\mathbf{II_c}$ gave 11-(*p*-chlorophenyl)-7,8,9,10-tetrahydroquinolino[3′,2′:4,5]thieno[3,2-d]-1,2,3-triazin-4(3H)-one (**XXIII**) which reacted with methyl iodide, *p*-methylphenacyl bromide and/or ethyl chloroacetate to give the corresponding *N*-alkylated products (**XXIV–XXVI**).



$\mathbf{II_c}$ XXIII

XXIV, R=CH_3

XXV, R=CH_2CO-C$_6$H$_4$-CH_3

XXVI, R=$CH_2CO_2C_2H_5$

The structures of the new compounds were confirmed on the basis of their elemental analyses and spectroscopic data (Tables I, II).

EXPERIMENTAL

All melting points were determined on a Kofler melting point apparatus and are uncorrected. IR spectra were obtained using a Pye-Unicam SP3-100 infrared spectrophotometer. NMR spectra were recorded on a Varian EM-390 90 MHZ spectrometer using TMS as internal standard. The elemental analyses were carried out on an elemental analyzer 240 C.

Synthesis of 2-methyl-11-(p-chlorophenyl)-7,8,9,10-tetrahydroquinolino-[3′,2′:4,5]thieno[3,2-d]oxazin-4-one (**IV**). Compound $\mathbf{II_a}$ (3.879, 0.01 mole) in alcoholic sodium hydroxide solution (100 ml, 5%) was refluxed for 2 hrs. The sodium salt (**III**) thus precipitated after cooling was collected by filteration, washed with ethanol and dried in air. The sodium salt (3.5 g) was refluxed for 4 hrs. with acetic anhydride (100 ml). The reaction mixture was concentrated by distillation and allowed to cool. The crystalline solid obtained (yield, 2.8 g, 73%) was applied in the next reactions without further purification. A sample was recrystallized from absolute ethanol as colourless needles mp 220–2°C.

Anal. Calcd. For $C_{20}H_{15}ClN_2O_2S$: C, 62.74; H, 3.95; N, 7.32; S, 8.37; Cl, 9.26%; Found: C, 62.80; H, 4.11; N, 7.29; S, 8.50; Cl, 9.60%.

Synthesis of 2-methyl-11-(p-chlorophenyl)-7,8,9,10-tetrahydroquinolino[3′,2′:4,5]thieno[3,2-d]pyrimidin-4(3H)-one (**V**). A mixture of oxazinone derivative (**IV**) (3.8 g, 0.01 mole) and ammonium acetate (1.54 g, 0.02 mole) in glacial acetic acid (50 ml) was refluxed for 3 hrs. The cooled reaction mixture

TABLE I

Important IR bands (ν in cm^{-1}) of the new compounds **(IV–XXVI)**

	νNH	νC≡N	νC=O	νC=S
IV	-	-	1750	-
V	3200-2400	-	1650	-
VI	-	-	1660	-
	-	-	1730,1660	-
VIII	3300,320(NH_2)	-	1660	-
IX	-	-	1680	-
X	-	-	1680	-
XI	-	2210	-	-
XII	3360,3200(NH_2)3100(NH)	-	-	-
XIII	-	-	-	-
XIV	-	2200	1720,1700	-
XV	3210-3150	2200	1660	-
XVI	-	-	-	-
XVII	3360	-	1680	1150
XVIII	-	-	1670	-
XIX	3390,3150	-	1700-1680	-
XXI	3360,3100	-	1670	1150
XXII	-	-	1660	-
XXIII	3200-2400	-	1650	-
XXIV	-	-	1650	-
XXV	-	-	1680,1660	-
XXVI	-	-	1740,1660	-

was diluted with water whereby a white compound precipitated. It was collected by filtration, dried and recrystallized from DMF as white crystals mp. 370–5°C, yield 2.6 g (68%).

Anal. Calcd. For $C_{20}H_{16}ClN_3OS$: C, 62.91; H, 4.22; N, 11.00 S, 8.40; Cl, 9.28%; Found: C, 63.04; H, 4.19; N, 10.77; S, 8.37; Cl, 9.11%.

Alkylation of 2-methyl-11-(p-chlorophenyl)-7,8,9,10-tetraroquinolino-[3',2':4,5]thieno[3,2-d]pyrimidin-4(3H)-one **(V)**; *formation of* **(IV)** & **(VII)**. General procedure. A solution of **(V)** (0.76 g, 0.002 mole) in DMF (15 ml) was stirred for 5 mins. with potassium carbonate (0.5 g), and then alkylating agent (0.0025 mole) in DMF (10 ml) was added. The reaction mixture was stirred for 2 hrs. at room temperature and then diluted with water. The precipitate thus obtained was crystallized from ethanol as colourless needles. In this way the following compounds were prepared:

TABLE II

^{1}H-NMR spectra of most of the synthesized compounds

Compd. No (Solvent)	Aromatic protons	$-CH_2-$ at C-7 (t)	$-CH_2$ at C-10 (t)	$-(CH_2)_2-$ at C-8,9 (m)	Other signals
IV ($CDCl_3$)	7.00-7.50(q,3H)	3.00-3.20	2.40-2.60	1.50-2.00	2.10(s,3H,CH_3).
V ($CDCl_3$)	7.05-7.60(q,4H)	3.25-3.50	2.55-2.80	1.65-2.15	2.30(s,3H,CH_3).
VI ($CDCl_3$)	7.05-7.50(q,4H)	3.05-3.25	2.45-2.70	1.60-2.10	2.30(s,3H,CH_3) 3.50(s,3H, N-CH_3).
VIII ($CDCl_3$)	6.95-7.45(q,4H)	3.00-3.20	2.40-2.60	1.55-2.05	2.30(s,3H,CH_3) 5.00(s,2H,NH_2 and exchangeable with D_2O).
IX (CF_3CO_2D)	two quartets at 8.10-8.50(4H), 7.40-7.80(4H)	2.30-2.55	2.70-2.95	1.80-2.30	2.60(s,3H,CH_3) 9.10(s,1H,N=CH).
X ($CDCl_3$)	7.10-7.50(m,9H)	3.10-3.30	2.50-2.70		1.65-2.20(m,7H,4H of $(CH_2)_2$ at C-8,9 and 3H of CH_3 group).
XI ($CDCl_3$)	6.90-7.55(m,5H; 4H aromatic and 1H of -N=CH-)	(2.95-3.20)[a]	(2.30-2.50)[b]	(1.55-2.10)[c]	3.40-3.70(q,2H,OCH_2) 1.10-1.30(t,3H,CH_3).
XII (DMSO)	7.60-7.50(q,4H)	2.90-3.10		1.60-2.00	4.80(s,2H,NH_2). 7.90(s,1H,CH-pyrimidine).

TABLE II (*Continued*)

XIII ($CDCl_3$)	7.10-7.60(q,4H)	(3.30-3.55)[d]	(2.55-2.80)[e]	(1.65-2.20)[f]	8.60(s,1H,CH-pyrimidine). 9.20(s,1H,CH-triazole).
XIV ($CDCl_3$)	6.85-7.50(q,4H)	(3.00-3.25)[a]	(2.30-2.55)[b]	(1.55-2.00)[c]	2.05(s,6H, two CH_3CO).
XIV ($CDCl_3$)	7.05-7.55(q,4H)	(3.00-3.25)[a]	(2.30-2.55)[b]	(1.65-2.05)[c]	1.55(3H,CH_3CO) 6.60(1H,NH, and exchangeable with D_2O).
XVIII ($CDCl_3$)	7.10-7.65(q,4H)	3.20-3.40	2.50-2.70	1.70-2.10	0.90-1.15(t,3H,CH_3) 0.10-2.40(q,2H,SCH_2).
XXII ($CDCl_3$)	7.10-7.50(q,4H)	3.00-3.25	2.40-2.65		1.60-2.10(m,7H,4H of $-(CH_2)_2-$at C-8,9 and 3H of SCH_3). 3.50(s,3H,N-CH_3).
XXIII (CF_3CO_2D)	7.20-7.70(q,4H)	3.35-3.60	2.65-2.90	1.70-2.30	
XXIV ($CDCl_3$)	7.15-7.55(q,4H)	3.10-3.35	2.50-2.75	1.70-2.20	4.00(s,3H,N-CH_3).
XXV ($CDCl_3$)	7.15-7.95(m,8H)	3.05-3.30	2.50-2.75	1.65-2.15	5.75(s,2H,NCH_2) 2.40(s,3H,CH_3).
XXVI ($CDCl_3$)	7.10-7.50(q,4H)	3.10-3.35	2.50-2.75	1.65-2.15	5.15(s,2H,NCH_2) 4.10-4.40(q,2H,CH_2CH_3) 1.20-1.40(t,3H,CH_2CH_3)

[a] CH_2 at C-8.
[b] CH_2 at C-5.
[c] $-(CH_2)_2-$ at C-6, 7.
[d] CH_2 at C-11.
[e] CH_2 at C-8.
[f] $-(CH_2)_2-$ at C-9, 10.

a) 2,3-Dimethyl-11-(p-chlorophenyl)-7,8,9,10-tetrahydroquinolino-[3',2':4,5]thieno[3,2-d]pyrimidin-4(3H)-one (**VI**). Obtained from (**V**) and methyl iodide in 60% yield, mp. 260–63°C.

Anal. Calcd. for $C_{21}H_{18}ClN_3OS$: C, 63.71; H, 4.58; N, 10.61; S, 8.10; Cl, 8.96%; Found: C, 63.31; H, 4.56; N, 10.97; S, 8.00; Cl, 9.00%.

b) 3-Ethoxycarbonylmethyl-2-methyl-11-(p-chlorophenyl)-7,8,9,10-tetrahydroquinolino[3',2':4,5]thieno[3,2-d]pyrimidin-4(3H)-one (**VII**). Obtained from (**V**) and ethyl chloroacetate in 67% yield, mp. 210°C.

Anal. Calcd. for $C_{24}H_{22}ClN_3O_3S$: C, 61.60; H, 4.74; N, 8.98; S, 6.85; Cl, 7.85%; Found: C, 61.32; H, 4.65; N, 9.11; S, 7.00; Cl; 7.69%.

Synthesis of 3-amino-2-methyl-11-(p-chlorophenyl)-7,8,9,10-tetrahydroquinolino[3',2':4,5]thieno[3,2-d]-pyrimidin-4(3H)-one (**VIII**). A mixture of oxazinone (**IV**) (3.8 g, 0.01 mole) and hydrazine hydrate (1 ml, 0.02 mole) was refluxed in ethanol (50 ml) for 2 hrs. The product thus obtained was recrystallized from ethanol to give (**VIII**) as colourless needles mp, 235–7°C, yield 3.3 g (83%).

Anal. Calcd. for $C_{20}H_{17}ClN_4OS$: C, 60.53; H, 4.32; N, 14.12; S, 8.08; Cl, 8.93%; Found: C, 60.43; H, 4.38; N, 14.06; S, 8.29; Cl, 9.31%.

Synthesis of 2-methyl-11-(p-chlorophenyl)-3-(p-nitrobenzylideneamino)-7,8,9,10-tetrahydroquinolino-[3',2':4,5]thieno[3,2-d]pyrimidin-4(3H)-one (**IX**). To a mixture of (**VIII**) (0.8 g, 0.002 mole) and *p*-nitrobenzaldehyde (0.3 g, 0.002 mole) in ethanol (20 ml), a few drops of piperidine were added. The mixture was refluxed for 3 hrs. and the solid thus formed while hot was collected and recrystallized from DMF as yellow needles mp. 290–2°C, yield 0.75 g (70%).

Anal. Calcd. for $C_{27}H_{20}ClN_5O_3S$: C, 61.19; H, 3.80; N, 13.21; S, 6.05; Cl, 6.69%; Found: C, 61.39; H, 3.70; N, 13.00; S, 6.11; Cl, 6.81%.

Synthesis of 2-methyl-11-(p-chlorophenyl)-3-phenyl-7,8,9,10-tetrahydroquinolino[3',2':4,5]thieno[3,2-d]pyrimidin-(3H)-one (**X**). A mixture of oxazinone derivative (**IV**) (0.77 g, 0.002 mole) and aniline (0.4 ml, 0.004 mole) in glacial acetic acid (30 ml) was refluxed for 4 hrs. On cooling and dilution with water a white solid precipitated. It was filtered off and recrystallized from ethanol as white needles mp. 268–71°C, yield 0.78 g (85%).

Anal. Calcd. for $C_{26}H_{20}ClN_3OS$: C, 68.19; H, 4.40; N, 9.18; S, 7.00; Cl, 7.74%; Found: C, 68.15; H, 4.45; N, 9.01; S, 7.16; Cl, 7.71%.

Synthesis of ethyl N-[4-(p-chlorophenyl)-2-cyano-5,6,7,8-tetrahydrothieno[2,3-b]quinolin-3-yl]methanimidate (**XI**). A mixture of $\mathbf{II_b}$ (3.4 g, 0.01 mole), triethyl orthoformate (0.01 mole) and acetic anhydride (20 ml) was refluxed for 5 hrs. After cooling a colourless crystalline compound was formed. It was filtered off and recrystallized from ethanol mp. 240–242°C, yield (87%).

Anal. Calcd. for $C_{21}H_{18}ClN_3OS$: C, 63.71; H, 4.58; N, 10.61; S, 8.10; Cl, 8.96%; Found: C, 64.10; H, 4.64; N, 10.95; S, 8.01; Cl, 9.13%.

Synthesis of 4-imino-11-(p-chlorophenyl)-7,8,9,10-tetrahydroquinolino-[3',2':4,5]thieno[3,2-d]pyrimidin-3(4H)-amine (**XII**). To a suspension of compound (**XI**) (2 g, 0.005 mole) in ethanol (50 ml), hydrazine hydrate (0.5 ml, 0.01 mole) was added. The mixture was refluxed on a water bath for one hour, concentrated and allowed to stand overnight. The precipitate formed was filtered off, dried and recrystallized from an ethanol-chloroform mixture to give fine needles mp. 290–93°C, yield 1 g (52%).

Anal. Calcd. for $C_{19}H_{16}ClN_5S$: C, 59.76; H, 4.22; N, 18.34; S, 8.40; Cl, 9.28%; Found: C, 60.00; H, 4.36; N, 18.54; S, 8.21; Cl, 9.17%.

Synthesis of 7-(p-chlorophenyl)-8,9,10,11-tetrahydroquinolino[3',2':4,5]-thieno[2,3-e]-s-triazolo[2,3-c]pyrimidine (**XIII**).

a) From (**XII**) *and formic acid.* Compound (**XII**) (0.38 g, 0.001 mole) was refluxed in excess of formic acid (10 ml) for 8 hrs. The cooled reaction mixture was diluted with water, the precipitated solid was collected and crystallized from ethanol to give white crystals mp. 275–6°C; yield 0.28 g (72%).

Anal. Calcd. for $C_{20}H_{14}ClN_5S$: C, 61.30; H, 3.60; N, 17.87; S, 8.18; Cl, 9.05%; Found: C, 61.41; H, 3.35; N, 17.93; S, 8.00; Cl, 9.00%.

b) From (**XII**) *and ethyl formate.* A mixture of compound (**XII**) (0.38 g, 0.001 mole) and ethyl formate (15 ml) was heated on a water bath for 10 hrs. The excess of ethyl formate was removed by distillation in vacuum. The residue was crystallized from ethanol as white crystals, mp. 275–7°C, yield 0.3 g (77%).

c) From **(XII)** *and triethyl orthoformate/DMF.* A mixture of **(XII)** (0.38 g, 0.001 mole) and equimolar amount of triethyl orthoformate in dimethyl formamide (10 ml) was refluxed for one hour. After cooling and dilution with water, the precipitated product was collected and crystallized from ethanol as white crystals mp. 275–6°C, yield 0.33 g (85%).

Reaction of 3-amino-4-(p-chlorophenyl)-5,6,7,8-tetrahydrothieno-[2,3-b]quinoline-2-carbonitrile **(II_b)** *with acetic anhydride.* A mixture of **(II_b)** (3.4 g, 0.01 mole) and redistilled acetic anhydride (40 ml) was refluxed for 4 hrs. The reaction mixture was diluted with water whereby a white precipitate was obtained. It was collected and crystallized from 40 ml of ethanol as colourless needles. Recrystallization again from ethanol gave colourless needles mp. 225–6°C, yield 1.7 g (40%). This compound was identified as 3-(diacetylamino)-4-(*p*-chlorophenyl)-5,6,7,8-tetrahydro-thieno[2,3-b]-quinoline-2-carbonitrile **(XIV)**.

Anal. Calcd. for $C_{22}H_{18}ClN_3O_2S$: C, 62.33; H, 4.28; N, 9.91; S, 7.56; Cl, 8.36%; Found: C, 62.00; H, 4.51; N, 10.00; S, 7.50; Cl, 8.61%.

The filtrate from the first crystallization was diluted with water (50 ml) to give a white precipitate which was collected and crystallized from benzene as white crystals mp. 210–212°C, yield 1.33 (35%). This product was identified as 3-acetylamino-4-(*p*-chlorophenyl)-5,6,7,8-tetrahydro-thieno[2,3-b]quinoline-2-carbonitrile **(XV)**.

Anal. Calcd. for $C_{20}H_{16}ClN_3OS$: C, 62.91; H, 4.22; N, 11.00; S, 8.40; Cl, 9.28%; Found: C, 62.70; H, 4.39; N, 11.17; S, 8.77; Cl, 9.52%.

Synthesis of 2-methyl-4-methoxy-11-(p-chlorophenyl)-7,8,9,10-tetrahydroquinolino[3',2';:4,5]-thieno-[3,2-d]pyrimidine **(XVI)**. Compound **(XV)** (0.76 g, 0.002 mole) in sodium methoxide solution (0.1 g sodium/30 ml methanol) was reflixed for 2 hrs. On concentration and cooling a white solid was obtained. It was recrystallized from ethanol as white needles mp. 195–7°C, yield 0.6 g (75%).

Anal. Calcd. for $C_{21}H_{18}ClN_3OS$: C, 63.71; H, 4.58; N, 10.61; S, 8.10; Cl, 8.96%; Found: C, 63.56; H, 4.46; N, 10.81; S, 8.00; Cl, 9.00%.

Synthesis of 11-(p-chlorophenyl)-3-phenyl-2-thioxo-7,8,9,10-tetrahydroquinolino[3',2':4,5]thieno[3,2-d]pyrimidin-4(1H,3H)-one **(XVII)**. An equimolar mixture of **(II_c)** (0.71 g, 0.002 mole) and phenyl isothiocyanate (0.002 mole) in acetic acid (15 ml) was heated on a steam bath for 8 hrs. The reaction mixture was cooled to room temperature and the crystalline product that separated out was filtered, dried and recrystallized from acetic acid as yellow needles mp. 335–6°C; yield 0.77 g (81%).

Anal. Calcd. for $C_{25}H_{18}ClN_3OS_2$: C, 63.08; H, 3.81; N, 8.83; S, 13.47; Cl, 7.45%; Found: C, 63.00; H, 4.21; N, 8.80; S, 13.76; Cl, 7.22%.

Synthesis of 2-ethylthio-11-(p-chlorophenyl)-3-phenyl-7,8,9,10-tetrahydroquinolino[3',2':4,5]thieno[3,2-d]pyrimidin-4(3H)-one **(XVIII)**. Compound **(XVII)** (2.4 g, 0.005 mole) was dissolved in 30 ml of 4% ethanolic sodium hydroxide solution. To this solution ethyl iodide (1.56 g, 0.01 mole) was added. The reaction mixture was refluxed on a water bath for one hour. On cooling, the precipitated solid was filtered off and recrystallized from ethanol as white needles mp. 332–3°C, yield 1.76 g (70%).

Anal. Calcd. for $C_{27}H_{22}ClN_3OS_2$: C, 64.34; H, 4.40; N, 8.34; S, 12.72; Cl, 7.03%; Found: C, 64.00; H, 4.37; N, 8.07; S, 13.00; Cl, 7.06%.

Synthesis of 1-(3-carbamoyl-4-(p-chlorophenyl)-5,6,7,8-tetrahydrothieno[2,3-b]quinolin-2-yl)-3-phenylurea **(XIX)**. A mixture of **(II_c)** (0.71 g, 0.002 mole) and phenyl isocyanate (0.002 mole) in acetic acid (20 ml) was heated on a steam bath for 2 hrs. The white precipitate was collected and crystallized from DMF mp. 375–80°C, yield 0.86 g (90%).

Anal. Calcd. for $C_{25}H_{21}ClN_4O_2S$: C, 62.95; H, 4.44; N, 11.75; S, 6.72; Cl, 7.43%; Found: C, 62.90; H, 4.49; N, 11.48; S, 6.90; Cl, 7.20%.

Synthesis of 11-(p-chlorophenyl)-2-thioxo-7,8,9,10-tetrahydroquinolino-[3',2':4,5]thieno[3,2-d]pyrimidin-4-(1H,3H)-one **(XXI)**. A mixture of **(II_c)** (0.71 g, 0.002 mole) and carbon disulfide (3 ml) in dry pyridine (30 ml) was heated on a water bath for 6 hrs, during reaction time hydrogen sulfide was evolved. The solvent was removed by distillation under reduced pressure and the residue was crystallized from DMF/H_2O as faint pink needles mp. 350–2°C; yield 0.48 g (60%).

Anal. Calcd. for $C_{19}H_{14}ClN_3OS_2$: C, 57.07; H, 3.35; N, 10.51; S, 16.03; Cl, 8.87%; Found: C, 57.15; H, 3.42; N, 10.30; S, 16.00; Cl, 9.09%.

Synthesis of 2-methylthio-3-methyl-11-(p-chlorophenyl)-7,8,9,10-tetrahydroquinolino[3',2':4,5]thieno-[3,2-d]pyrimidin-4(3H)-one **(XXII)**. To a suspension of **(XXI)** (2.0 g, 0.005 mole) and anhydrous sodium acetate (2 g) in ethanol (50 ml), (2.8 g, 0.02 mole) of methyl iodide was added. The reaction mixture was refluxed for 2 hrs. On cooling, the precipitated solid was collected and crystallized from ethanol as white needles. mp. 240–2°C, yield 1.5 g (70%).

Anal. Calcd. For $C_{21}H_{18}ClN_3OS_2$: C, 58.94; H, 4.24; N, 9.82; S, 14.98; Cl, 8.28%; Found: C, 58.49; H, 4.13; N, 9.80; S, 15.06; Cl, 8.41%.

Reaction of 3-amino-4-(p-chlorophenyl)-5,6,7,8-tetrahydro-thieno-[2,3-b]quinoline-2-carboxamide (**II_c**) *with acetic anhydride.* A mixture of **II_c** (3.6 g, 0.01 mole) and redistilled acetic anhydride (50 ml) was refluxed for 5 hrs. The solid which precipitated after cooling was filtered off and recrystallized from ethanol-chloroform mixture as white crystals mp. 370–375°C. yield, 1.15 g (30%). This compound was identified as 2-methyl-11-(*p*-chlorophenyl)-7,8,9,10-tetrahydroquinolino[3',2':4,5]thieno[3,2-d]-pyrimidin-4(3H)-one (**V**) which was previously prepared by reaction of oxazinone derivative (**IV**) with ammonium acetate and acetic acid.

Anal. Calcd. for $C_{20}H_{16}ClN_3OS$: C, 62.91; H, 4.22; N, 11.00; S, 8.40; Cl, 9.28%; Found: C, 63.11; H, 4.20; N, 11.37; S, 8.50; Cl, 9.50%.

The filtrate from the above crude product was diluted with water (100 ml) to give a white precipitate which was collected and crystallized from ethanol as colourless needles mp. 225–6°C, yield 2.12 g (50%). The structure of this product was assigned as 3-(diacetylamino)-4-(*p*-chlorophenyl)-5,6,7,8-tetrahydro-thieno-[2,3-b]quinoline-2-carbonitrile (**XIV**) which was also obtained by direct acetylation of compound (**II_b**) with acetic anhydride.

Anal. Calcd. for: $C_{22}H_{18}ClN_3O_2S$: C, 62.33; H, 4.28; N, 9.91; S, 7.56; Cl, 8.36%; Found: C, 62.39; H, 4.15; N, 10.16; S, 7.30; Cl, 8.00%.

Synthesis of 11-(p-chlorophenyl)-7,8,9,10-tetrahydroquinolino-[3',2':4,5]thieno[3,2-d]-1,2,3-triazin-4(3H)-one (**XXIII**). To a cold solution of (**II_c**) (2 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 was filtered off and crystallized from chloroform as white crystals mp. 210–212°C, yield 1.7 g (82%).

Anal. Calcd. for $C_{18}H_{13}ClN_4OS$: C, 58.62; H, 3.55; N, 15.19; S, 8.69; Cl, 9.61%; Found: C, 58.66; H, 3.40; N, 15.01; S, 8.90; Cl, 9.86%.

Alkylation of 11-(p-chlorophenyl-7,8,9,10-tetrahydroquinolino-[3',2':4,5]thieno[3,2-d]-1,2,3-triazin-4(3H)-one (**XXIII**)*; formation of* (**XXIV–XXVI**). A solution of triazinone derivative (**XXIII**) (0.74 g, 0.002 mole) in DMF (15 ml) was stirred for a while with potassium carbonate (0.5 g), and then the alkylating agent (0.0025 mole) in DMF (10 ml) was added. The reaction mixture was stirred for 2 hrs. at room temperature and then diluted with water. The precipitate thus formed was filtered off, dried and crystallized from a suitable solvent. In this way, the following compounds were synthesized:

a) 3-Methyl-11-(p-chlorophenyl)-7,8,9,10-tetrahydroquinolino-[3',2':4,5]thieno[3,2-d]-1,2,3-triazin-4-4(3H)-one (**XXIV**). Obtained from (**XXIII**) and methyl iodide in 70% yield. It was crystallized from ethanol as colourless needles mp. 260–63°C.

Anal. Calcd. for $C_{19}H_{15}ClN_4OS$: C, 59.61; H, 3.95; N, 14.63; S, 8.37; Cl, 9.26%; Found: C, 59.66; H, 3.96; N, 14.51; S, 8.00; Cl, 9.20%.

b) 11-(p-Chlorophenyl)-3-(p-methylphenacyl)-7,8,9,10-tetrahydroquinolino[3'2':4,5]thieno[3,2-d]-1,2,3-triazin-4(3H)-one (**XXV**). Obtained from **XXIII** and *p*-methylphenacyl bromide in 81% yield. It was crystallized from ethanol-chloroform mixture into buff crystals mp. 250–251°C.

Anal. Calcd. for $C_{27}H_{21}ClN_4O_2S$: C, 64.73; H, 4.22; N, 11.18; S, 6.40; Cl, 7.08%, Found: C, 64.91; H, 4.27; N, 11.43; S, 6.56; Cl, 7.00%.

c) 3-Ethoxycarbonylmethyl-11-(p-chlorophenyl)-7,8,9,10-tetrahydroquinolino[3',2':4,5]thieno[3,2-d]-1,2,3-triazin-4(3H)-one (**XXVI**). Obtained from **XXIII** and ethyl chloroacetate in 73% yield. It was crystallized from ethanol in the form of colourless plates mp. 190°C.

Anal. Calcd. for $C_{22}H_{19}ClN_4O_3S$: C, 58.09; H, 4.21; N, 12.32; S, 7.05; Cl, 7.79%; Found: C, 58.11; H, 4.00; N, 12.31; S, 7.20; Cl, 8.00%.

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