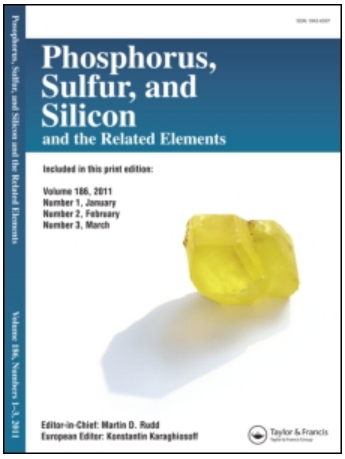

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SYNTHESIS OF THIENOQUINOLINES. PART II. SYNTHESIS OF NOVEL TETRAHYDROQUINOLINO[3',2':4,5]THIENO[3,2-d]-PYRIMIDINE DERIVATIVES

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SYNTHESIS OF THIENOQUINOLINES. PART II. SYNTHESIS OF NOVEL TETRAHYDROQUINOLINO[3',2':4,5]THIENO[3,2-d]-PYRIMIDINE DERIVATIVES

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The key compound, 11-*p*-chlorophenyl-7,8,9,10-tetrahydroquinolino[3',2':4,5]thieno[3,2-d]pyrimidin-4(3H)-one (**2**) was prepared and reacted with methyl iodide to give the N-methyl derivative (**3**). Also, reaction of 2 with phosphours oxychloride yielded 4-chloro-11-*p*-chlorophenyl-7,8,9,10-tetrahydroquinolino[3',2':4,5]thieno[3,2-d]pyrimidine (**4**) which, in turn, underwent reactions with thiourea, aniline, piperidine, morpholine, 1-methylpiperazine and/or hydrazine hydrate to afford the corresponding 4-substituted pyrimidine derivatives 5, 7, 8, 9, 10 and 11 respectively. Methylation of 5 yielded thioether 6. Furthermore, reaction of 4 with sodium azide gave tetrazolo derivative 12 which was also obtained by diazotisation of 11. The structure of all new compounds was confirmed by elemental and spectral analyses (ir, nmr).

Key words: Chloro-; anilino-; morpholinyl-; piperazinyl-; hydrazino- and tetrazolothienotetrahydroquinolino pyrimidines.

Pyrimidines have occupied a unique place and have remarkably contributed to biological and medicinal chemistry. Various analogues of thiopyrimidines possess effective antibacterial, antifungal, antiviral, insecticidal and miticidal activities.[1–3] On the other hand, an exhaustive search through the Chemical Abstracts showed that only two quinolino[3',2':4,5]thieno[3,2-d]pyrimidine derivatives have been reported.[4,5] In view of these facts and as a continuation of our previous work about the synthesis and applications as antimicrobial agents of thienoquinoline derivatives,[6–9] we report in this paper the synthesis of novel tetrahydroquinolino[3',2':4,5]thieno[3,2-d]pyrimidine derivatives.

The key intermediate and related derivatives reported in this paper were obtained according to the Scheme I, starting from 3-amino-4-(*p*-chlorophenyl)-5,6,7,8-tetrahydro-thieno[2,3-b]quinoline-2-carboxamide (**1**). Refluxing of 1 with triethyl orthoformate in acetic anhydride gave the new pyrimidone (**2**) which was methylated to yield the N-methyl derivative (**3**). Treatment of 2 with phosphorus oxychloride readily yielded 4-chloro-11-(*p*-chlorophenyl)-7,8,9,10-tetrahydroquinolino[3',2':4,5]thieno[3,2-d]pyrimidine (**4**) which has served as a facile point of departure into the desired compounds.

Thus, interaction of 4 with thiourea gave the 4-mercapto derivative (**5**). The ir spectrum of 5 indicated bands at 3160 and 1580 cm^{-1} suggesting that it existed as a tautomeric mixture of 5 and the corresponding thiono-form. Methylation of 5 produced the S-methyl derivative (**6**). When 4 was boiled with amines (aniline,

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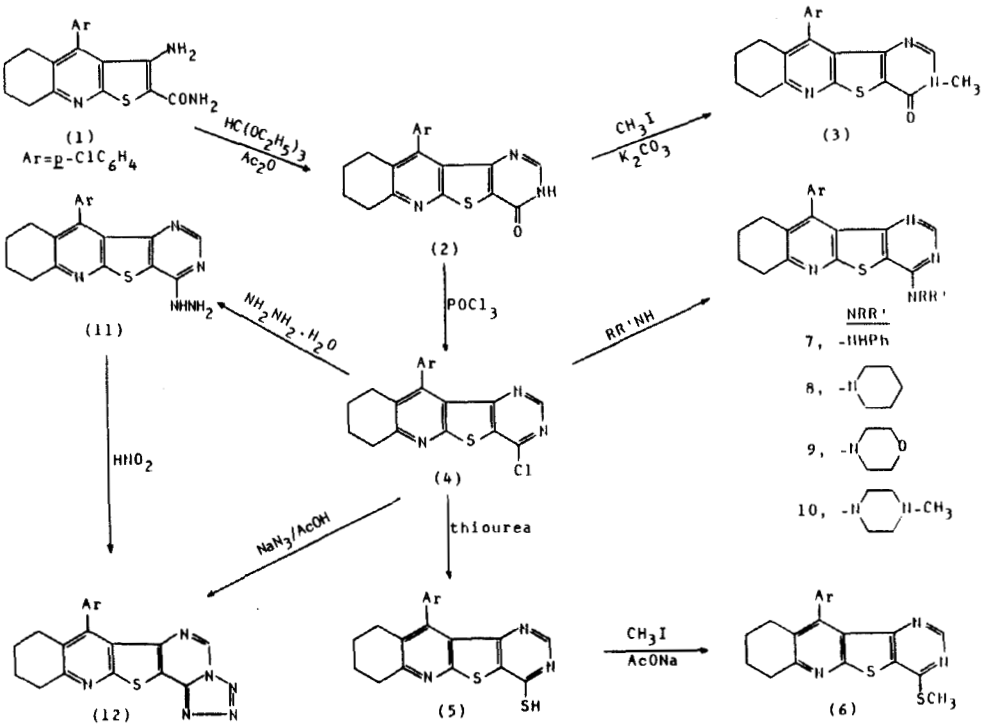

SCHEME I

TABLE I

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

Compd. No.	IR (Selected bands)	^{1}H-NMR (in $CDCl_3$)
2	3200-2400(NH) and 1640(CO)	7.80(s,1H,CH-pyrimidine), 3.05-3.30(t,2H,CH_2 at C-7), 2.45-2.70(t,2H,CH_2 at C-10), 1.65-2.15 (m,4H,$(CH_2)_2$ at C-8,9) and 7.10-7.55(q,4H, Ar-H).
3	1650(CO)	7.80(s,1H,CH-pyrimidine), 3.60(s,3H,NCH_3), 3.05-3.30(t,2H,CH_2 at C-7), 2.45-2.70(t,2H,CH_2 at C-10), 1.65-2.15(m,4H,$(CH_2)_2$ at C-8,9) and 7.10-7.55(q,4H,Ar-H).
4	1590(C=N)	8.70(s,1H,CH-pyrimidine), 3.05-3.30(t,2H,CH_2 at C-7), 2.45-2.70(t,2H,CH_2 at C-10), 1.55-2.10 (m,4H,$(CH_2)_2$ at C-8,9) and 7.05-7.55(q,4H,Ar-H).
5	3160(NH)	8.00(s,1H,CH-pyrimidine), 3.25-3.55(t,2H,CH_2 at C-7), 2.65-2.70(t,2H,CH_2 at C-10), 1.85-2.35 (m,4H,$(CH_2)_2$ at C-8,9) and 7.30-7.75(q,4H,Ar-H).
6	-	8.60(s,1H,CH-pyrimidine), 3.05-3.30(t,2H,CH_2 at

TABLE I *(Continued).*

Compd. No.	IR (Selected bands)	^{1}H-NMR (in $CDCl_3$)
		C-7), 2.45-2.65(t,2H,CH_2 at C-10), 1.60-2.10 (m,4H,$(CH_2)_2$ at C-8,9), 2.70(s,3H,SCH_3) and 7.00-7.50(q,4H,Ar-H).
7	3600-2700	8.60(s,1H,CH-pyrimidine), 8.40(s,1H,NH), 3.00-3.25(t,2H,CH_2 at C-7), 2.40-2.65(t,2H,CH_2 at C-10), 1.55-2.10(m,4H,$(CH_2)_2$ at C-8,9) and 7.00-7.60(m,9H,Ar-H).
8	1600(C=N)	8.30(s,1H,CH-pyrimidine), 3.75-4.00(t,4H, CH_2 CH_2 >N- of piperidine ring), 1.3-1.60(m,6H,three methylene group of piperidine ring), 2.40-2.65 (t,2H,CH_2 at C-10), 3.00-3.25(t,2H,CH_2 at C-7), 1.65-2.15(m,4H,$(CH_2)_2$ at C-8,9) and 7.00-7.50 (q,4H,Ar-H).
9	1600(C=N)	8.30(s,1H,CH-pyrimidine), 3.75-4.00(t,4H, CH_2 CH_2 >N- of morpholine ring), 3.55-3.70(t,4H, CH_2 CH_2 >O of of morpholine ring), 2.40-2.65(t,2H,CH_2 at C-10), 3.00-3.25(t,2H,CH_2 at C-7), 1.60-2.10 (m,4H,$(CH_2)_2$ at C-8,9) and 7.00-7.50(q,4H,Ar-H).
10	1600(C=N)	8.30(s,1H,CH-pyrimidine), 3.75-4.00(t,4H, CH_2 CH_2 >N- of piperazine ring attached to heterocyclic system), 2.40-2.65(t,6H,4H of CH_2 CH_2 >N- and 2H of CH_2 at C-10), 3.00-3.25(t,2H,CH_2 at C-7), 2.30(s,3H,NCH_3), 1.60-2.10(m,4H,$(CH_2)_2$ at C-8,9) and 7.00-7.50(q,4H,Ar-H).
11	3340,3200, 3100($NHNH_2$) and 1630(C=N)	8.40(s,1H,CH-pyrimidine), 3.00-3.20(2H,CH_2 at C-7), 1.40-1.90(m,4H,$(CH_2)_2$ at C-8,9), 5.00 (s,2H,NH_2), 9.50(s,1H,NH) and 7.20-7.60(q,4H, Ar-H).
12	-	8.70(s,1H,CH-pyrimidine), 3.30-3.55(t,2H,CH_2 at C-11), 2.55-2.80(t,2H,CH_2 at C-8), 1.70-2.25 (m,4H,$(CH_2)_2$ at C-9,10) and 7.10-7.65(q,4H, Ar-H).

piperidine, morpholine and/or 1-methylpiperazine), the corresponding 4-substituted pyrimidines (7, 8, 9 and 10 respectively) were obtained. Similarly, reaction of 4 with hydrazine hydrate yielded 4-hydrazino-11-(*p*-chlorophenyl)-7,8,9,10-tetrahydroquinolino[3′,2′:4,5]thieno[3,2-d]pyrimidine (**11**).

Finally, diazotisation of 11 using sodium nitrite and hydrochloric acid produced the tetrazolo derivative 12. This compound was also available from the reaction of 4 with sodium azide. The ir spectrum of 12 does not show any characteristic band for the azido group at about 2000–2200 cm^{-1}, thus; it seems that in the solid state 12 has essentially the tetrazole structure represented without any demonstrable contribution of the possible azido form.

All the new compounds 2 to 12 were suitably characterized by elemental analysis and spectral data (ir, nmr), which were satisfactory for the expected data (Table I).

EXPERIMENTAL

Melting points were determined on a kofler apparatus and they are uncorrected. Elemental analyses were obtained using elemental analyser 240°C. The ir spectra were recorded on a Pye-Unicam SP3-100 infrared spectrophotometer using potassium bromide tablet technique; the frequencies were expressed in cm^{-1}. The ^{1}H-nmr spectra were obtained on a Varian EM-390 90 MHZ spectrometer, with TMS as internal standard; the chemical shifts are reported in ppm from TMS and are given in δ unites. The starting compound, 3-amino-4-(*p*-chlorophenyl)-5,6,7,8-tetrahydro-thieno[2,3-b]quinoline-2-carboxamide (**3**) was prepared by the literature method.[10]

Synthesis of 11-(p-chlorophenyl)-7,8,9,10-tetrahydroquinolino[3',2':4,5]thieno[3,2-d]pyrimidin-4(3H)-one (**2**). Triethyl orthoformate (10 g, 0.067 mole) and compound **1** (20.4 g, 0.057 mole) in redistilled acetic anhydride (250 ml) were heated at 120°C for one hour. The reaction mixture was cooled, the formed precipitate was collected and recrystallized from DMF as white needles. mp. 350–3°C, yield 30.5 g (83%).

Anal. Calcd. for $C_{19}H_{14}ClN_3OS$: (367.85) C, 62.04; H, 3.84; N, 11.42; S, 8.72; Cl, 9.64%; Found: C, 62.00; H, 3.70; N, 11.50; S, 8.96; Cl, 9.70%.

Synthesis of 3-methyl-11-(p-chlorophenyl)-7,8,9,10-tetrahydroquinolino[3',2':4,5]thieno[3,2-d]pyrimidin-4(3H)-one (**3**). A solution of (**2**), (0.74 g, 0.002 mole) in DMF (15 ml) was stirred for a while with potassium carbonate (0.5 g), and then methyl iodide (0.005 mole) was added. The reaction mixture was stirred for 2 hrs. at room temperature and then diluted with water. The precipitate thus formed was filtered and crystallized from ethanol, mp. 285–7°C; yield 0.53 g (70%).

Anal. Calcd. for $C_{20}H_{16}ClN_3OS$: (381.88) C, 62.91; H, 4.22; N, 11.00; S, 8.40; Cl, 9.28%; Found: C, 62.70; 4.22; N, 11.16; S, 8.11; Cl, 9.50%.

Synthesis of 4-chloro-11-(p-chlorophenyl)-7,8,9,10-tetrahydroquinolino[3',2':4,5]thieno[3,2-d]pyrimidine (**4**). A suspension of (**2**) (4 g) in an excess of phosphorus oxychloride (40 ml) was refluxed for 3 hrs. The cooled reaction mixture was poured with vigorous stirring into ice water. The solid thus separated was collected and crystallized from ethanol-chloroform into fine white needles, mp. 198–200°C, yield 3.5 g (83%).

Anal. Calcd. for $C_{19}H_{13}Cl_2N_3S$: (395.09) C, 59.08; H, 3.39; N, 7.25; S, 8.30; Cl, 18.36%; Found: C, 59.17; H, 3.45; N, 7.30; S, 8.47; Cl, 18.00%.

Synthesis of 11-(p-chlorophenyl)-7,8,9,10-tetrahydroquinolino[3',2':4,5]thieno[3,2-d]pyrimidin-4(3H)-thione (**5**). A mixture of chloro-compound (**4**) (0.77 g, 0.002 mole) and thiourea (0.3 g, 0.004 mole) in isopropanol (40 ml) was refluxed for 3 hrs. Upon cooling, the precipitated solid was collected, dissolved in warm 10% sodium hydroxide solution and filtered. On acidification of the filtrate with acetic acid, the yellow precipitate thus formed was collected and crystallized from chloroform as yellow needles mp. 289–292°C, yield 0.7 g (31%).

Anal. Calcd. for $C_{19}H_{14}ClN_3S_2$: (412.60) C, 59.44; H, 3.68; N, 10.95; S, 16.70; Cl, 9.23%; Found: C, 59.70; H, 3.71; N, 10.83; S, 16.50; Cl, 9.06%.

Synthesis of 4-methylthio-11-(p-chlorophenyl)-7,8,9,10-tetrahydroquinolino[3',2':4,5]thieno[3,2-d]pyrimidine (**6**). To a suspension of (**5**) (0.38 g, 0.001 mole) and sodium acetate (0.25 g, 0.003 mole) in ethanol (30 ml), methyl iodide (1 ml) was added. The resultant mixture was refluxed for one hour. On cooling, the precipitated product was filtered off and recrystallized from ethanol as colourless plates mp. 230–3°C, yield 0.32 g (80%).

Anal. Calcd. for $C_{20}H_{16}ClN_3S_2$: (365.89) C, 60.37; H, 4.05; N, 10.56; S, 16.11; Cl, 8.91%; Found: C, 60.30; H, 4.06; N, 10.40; S, 16.21; Cl, 8.76%.

Reaction of 4-chloro-11-(p-chlorophenyl)-7,8,9,10-tetrahydroquinolino[3',2':4,5]thieno[3,2-d]pyrimidine (**4**) *with different amines; formation of* (**7–10**).

General procedure. A mixture of chloro-compound (**4**) (0.39 g, 0.001 mole) and respective amine (10 ml) was refluxed for 3 hrs. Solvent was removed in vacuum and the residual solid was washed with water and crystallized from ethanol. In this way, the following compounds were prepared:

a) 4-Anilino-11-(p-chlorophenyl)-7,8,9,10-tetrahydroquinolino[3',2':4,5]thieno[3,2-d]pyrimidine (**7**). It was obtained from aniline in 84% yield, mp. 195–6°C.

Anal. Calcd. for $C_{25}H_{19}ClN_4S$: (442.84) C, 67.79; H, 4.32; N, 12.65; S, 7.24; Cl, 8.00%; Found: C, 67.66; H, 4.31; N, 12.80; S, 7.00; Cl, 8.00%.

b) 4-(1-Piperidinyl)-11-(p-chlorophenyl)-7,8,9,10-tetrahydroquinolino[3',2':4,5]thieno[3,2-d]pyrimidine (**8**). It was obtained from piperidine in 85% yield, mp. 200–203°C.

Anal. Calcd. for $C_{24}H_{23}ClN_4S$: (434.99) C, 66.27; H, 5.33; N, 12.88; S, 7.37; Cl, 8.15%; Found: C, 66.45; H, 5.39; N, 12.60; S, 7.50; Cl, 8.00%.

c) 4-(4-Morpholinyl)-11-(p-chlorophenyl)-7,8,9,10-tetrahydroquinolino[3',2':4,5]thieno[3,2-d]pyrimidine (**9**). It was obtained from morpholine in 91% yield, mp. 218–220°C.

Anal. Calcd. for $C_{23}H_{21}ClN_4OS$: (436.79) C, 63.22; H, 4.84; N, 12.82; S, 7.34; Cl, 8.11%; Found: C, 63.00; H, 4.79; N, 12.71; S, 7.03; Cl, 8.35%.

d) 4-(1-Methylpiperazin-4-yl)-11-(p-chlorophenyl)-7,8,9,10-tetrahydroquinolino[3',2':4,5]thieno[3,2-d]pyrimidine (**10**). It was obtained from 1-methylpiperazine in 93% yield, mp. 218–220°C.

Anal. Calcd. for $C_{24}H_{24}ClN_5S$: (450.21) C, 64.06; H, 5.38; N, 15.56; 7.12; Cl, 7.88%; Found: C, 64.00; H, 5.51; N, 15.63; S, 7.17; Cl, 8.06%.

Synthesis of 4-hydrazino-11-(p-chlorophenyl)-7,8,9,10-tetrahydroquinolino[3',2':4,5]thieno[3,2-d]pyrimidine (**11**). A mixture of chloro-compound (**4**) (3.9 g, 0.01 mole) and hydrazine hydrate (2 ml, 0.04 mole) in iso-propanol (50 ml) was refluxed for one hour. The product was collected and recrystallized from dioxane as white crystals, mp. 310–2°C, yield 3.4 g (89%).

Anal. Calcd. for $C_{19}H_{16}ClN_5S$: (417.25) C, 59.76; H, 4.22; N, 18.34; S, 8.40; Cl, 9.28%; Found: C, 60.11; H, 4.00; N, 18.25; S, 8.61; Cl, 9.50%.

Synthesis of 7-(p-chlorophenyl)-8,9,10,11-tetrahydroquinolino[3',2':4,5]thieno[2,3-e]tetrazolo[1,5-c]pyrimidine (**12**).

Method A:
To a solution of hydrazino-compound (**11**) (0.38 g, 0.002 mole) in concentrated hydrochloric acid (5 ml) and glacial acetic acid (5 ml) at 0°C, a cold solution of sodium nitrite (7 ml. 10%, 0.01 mole) was added with stirring during 10 minutes. The precipitate thus formed was filtered, washed with water and crystallized from acetic acid as colourless needles mp. 230–3°C, yield 0.35 g (90%).

Anal. Calcd. for $C_{19}H_{13}ClN_6S$: (428.31) C, 58.09; H, 3.34; N, 21.39; S, 8.16; Cl, 9.02%; Found: C, 58.15; H, 3.31; N, 21.07; S, 8.00; Cl, 9.27%.

Method B:
To a suspension of chloro-compound (**4**) (0.39 g, 0.001 mole) in acetic acid (50 ml), a solution of sodium azide (0.2 g) in water (5 ml) was added. The reaction mixture was refluxed for 4 hrs and concentrated to a small volume (20 ml). Cooling yielded a crystalline product which upon recrystallizatin was identical to that described in method A, yield 0.3 g (76%).

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