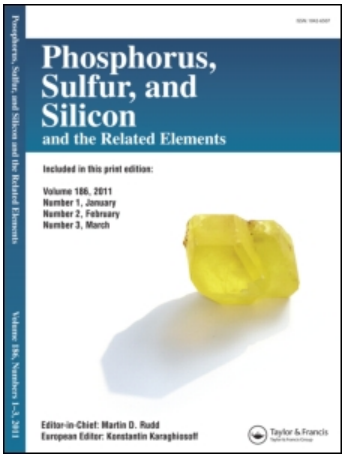

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SYNTHESIS OF THIENOQUINOLINES: PART III. SYNTHESIS OF NOVEL 4-HYDRAZINO-TETRAHYDROQUINOLINO[3′,2′:4,5]THIENO-[3,2-d]PYRIMIDINE DERIVATIVES

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Reaction of 4-hydrazino-11-(*p*-chlorophenyl)-7,8,9,10-tetrahydroquinolino[3′,2′:4,5]thieno[3,2-d]pyrimidine (**2**) with formic acid, acetic acid, diethylmalonate and/or carbon disulfide gave the corresponding s-triazolo derivatives (**3**, **4**, **9**) and (**10**) respectively. While acetylation of **2** yielded the triacetyl derivative (**5**). Also, condensation of **2** with aromatic aldehydes gave the hydrazones (**6a–c**) which cyclized easily into (**7a–c**). Moreover, acetylacetone was reacted with **2** to furnish the pyrazole derivative (**8**). The structural formula of these compounds was confirmed by elemental and spectral analyses data.

Key words: Methyl s-triazolo-; aryl s-triazolo-; triacetyl; hydrazono- and pyrazolyl-; tetrahydroquinolino-thieno-pyrimidines.

INTRODUCTION

Many of thienopyrimidin derivatives have been evaluated pharmacologically and found to show activity against diabetes mellitus,[1–3] and using as analgesics,[4] as antiflammants,[5] as sedatives[6] and as anticoagulants.[7] Literature survey revealed that only two quinolino[3′,2′:4,5]thieno[3,2-d]pyrimidine derivatives have been reported.[8,9] In view of these findings and as a continuation of our previous work on thienoquinolines,[10–14] we report herein the synthesis of other new tetrahydroquinoline thienopyrimidine derivatives.

RESULTS AND DISCUSSION

4-Hydrazino-11-(*p*-chlorophenyl)-7,8,9,10 -tetrahydroquinolino[3′,2′ : 4,5]thieno-[3,2-d]pyrimidine **2** seems to be a good starting material for such purpose.[15] It was prepared as reported in our previous paper.[14]

When hydrazino compound **2** was refluxed with formic and/or acetic acid, one-step ring closure occurred giving the corresponding s-triazolo derivatives (**3**) and (**4**) in good yields. Whereas refluxing of **2** with acetic anhydride does not give the expected s-triazolo compound **4** and instead of, the triacetyl derivative (**5**) was obtained.

Condensation of **2** with aromatic aldehydes in refluxing dioxane gave the corresponding hydrazones (**6a–c**) which were easily cyclized on treatment with thionyl chloride into 3-aryl-7-(*p*-chlorophenyl)-7,8,9,10-tetrahydroquinolino[3′,2′:4,5]thieno[2,3-e]-s-triazolo[4,3-c]pyrimidines (**7a–c**).

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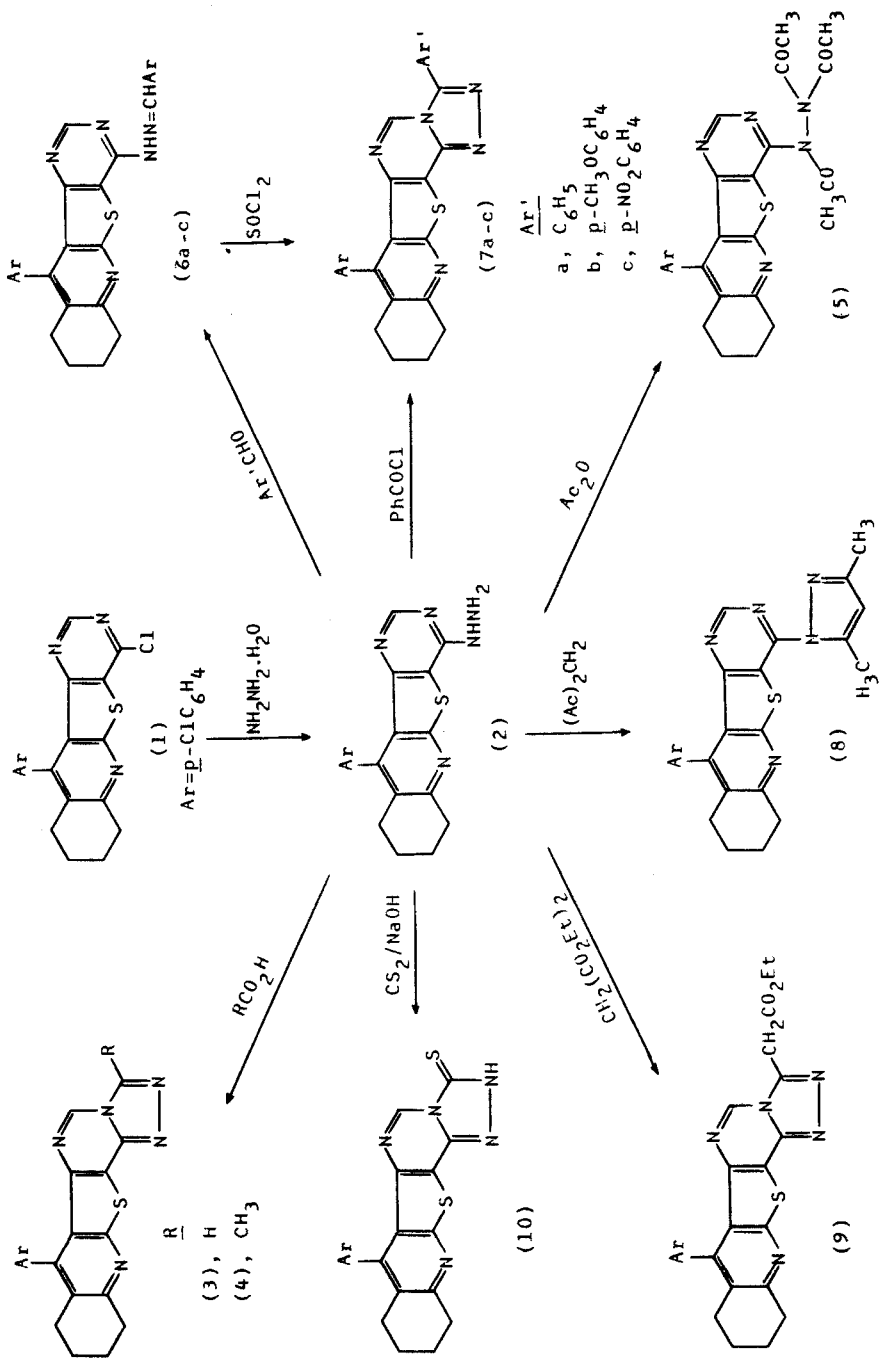

Scheme I.

TABLE I

The physical constants and analytical data of compounds **6a–c** and **7a–c**

Compd. No.	Ar	m.p °C	Yield %	Molecular formula	Analytical data Calcd./Found (%) C	H	N	S	Cl
6a,	C_6H_5	318-20	90	$C_{26}H_{20}ClN_5S$	66.45	4.29	14.90	6.82	7.54
					66.40	4.11	14.83	6.71	7.09
b,	p-CH_3O-C_6H_4	330-3	93	$C_{27}H_{22}ClN_5OS$	64.86	4.43	14.01	6.41	7.09
					64.80	4.39	14.12	6.69	7.00
c,	pNO_2-C_6H_4	334-5	97	$C_{26}H_{19}ClN_6O_2S$	60.64	3.72	16.32	6.23	6.88
					60.79	3.71	16.00	6.55	7.00
7a,	C_6H_5	265-6	86	$C_{26}H_{18}ClN_5S$	66.73	3.88	14.96	6.85	7.58
					66.52	3.91	14.82	6.77	7.90
b,	p-$CH_3OC_6H_4$	280-2	81	$C_{27}H_{20}ClN_5OS$	65.12	4.02	14.06	6.44	7.12
					65.00	4.13	14.20	6.35	7.19
c,	pNO_2-C_6H_4	297-9	83	$C_{26}H_{17}ClN_6O_2S$	60.88	3.34	16.38	6.25	6.91
					61.02	3.32	16.37	6.00	6.83

TABLE II

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

Compd. No.	IR (cm^{-1}) (Selected bands)	^{1}H-NMR (in $CDCl_3$)
3	-	8.95(s,1H,CH-triazole), 8.35(s,1H,CH-pyrimidine), 7.10-7.50(q,4H,Ar-H), 3.05-3.25(t,2H,CH_2 at C-11), 2.45-2.65(t,2H,CH_2 at C-8) and 1.60-2.10(m,4H, $(CH_2)_2$ at C-9,10.
4	-	8.35(s,1H,CH-pyrimidine), 7.10-7.50(q,4H,Ar-H), 3.05-3.25(t,2H,CH_2 at C-11), 2.75(s,3H,CH_3), 2.45-2.65(t,2H,CH_2 at C-8) and 1.60-2.10(m,4H, $(CH_2)_2$ at C-9,10).
5	1740 and 1720 for (C=O)	8.60(s,1H,CH-pyrimidine), 7.05-7.55(q,4H,Ar-H), 3.10-3.35(t,2H,CH_2 at C-7), 2.40-2.70(m,11H: 2H of CH_2 at C-10 and 9H of three acetyl groups and 1.65-2.15(m,4H, $(CH_2)_2$ at C-8,9).
6_b	3220-3200 for (NH)	8.45(s,1H,CH-pyrimidine), 8.65(s,1H, N=CH), 7.35-7.95(m,8H,Ar-H), 4.00(s,3H,OCH_3), 3.30-3.65 (t,2H,CH_2 at C-7), 2.65-2.80(t,2H,CH_2 at C-10) and 1.80-2.35(m,4H, $(CH_2)_2$ at C-8,9).
7_a	-	8.35(s,1H,CH-pyrimidine), 7.00-7.80(m,9H,Ar-H), 3.00-3.25(t,2H,CH_2 at C-11), 2.40-2.65(t,2H,CH_2 at C-8) and 1.50-2.00(m,4H, $(CH_2)_2$ at C-9,10).
8	-	8.60(s,1H,CH-pyrimidine), 7.10-7.55(q,4H,Ar-H), 6.00(s,1H,CH-pyrazole), 2.75(s,3H,CH_3),

TABLE II (*Continued*)

		2.40-2.65(2H, CH_2 at C-10), 2.30(s,3H, CH_3), 1.60-2.20(m,4H, $(CH_2)_2$ at C-8,9) and 3.00-3.25 (t,2H, CH_2 at C-7).
9	1740	8.85(s,1H,CH-pyrimidine), 7.05-7.50(q,4H,Ar-H), 4.05-4.40(q,2H,OCH_2), 1.30(t,3H,CH_3), 4.00 (s,2H,CH_2COO), 3.05-3.30(3H,CH_2 at C-11), 2.50-2.75(2H,CH_2 at C-8) and 1.60-2.15(4H,$(CH_2)_2$ at C-9,10).
10	3100(NH)	—

The cyclization of (**6a–c**) to (**7a–c**) using thionyl chloride proceeded according to the reported mechanism.[16] Further structural assignment of **7a–c** was carried out by independent synthesis of (**7a**) using another route via heating of the hydrazino compound **2** with benzoyl chloride under reflux. The two routes gave the same compound.

The reaction behaviour of hydrazino compound **2** towards dicarbonyl reagents was also investigated. Acetylacetone condensed with the terminal hydrazino group, when heated with **2** at refluxing temperature, to furnish 4-(3,5-dimethyl-pyrazol-1-yl)-11-(*p*-chlorophenyl)-7,8,9,10-tetrahydroquinolino[3′,2′:4,5]thieno[3,2-d]pyrimidine (**8**) in high yield. When **2** was heated with diethyl malonate a one step ring closure reaction occurred giving the s-triazolo compound (**9**).

Reaction of **2** with carbon disulfide in alcoholic sodium hydroxide produced the product, 7-(*p*-chlorophenyl)-8,9,10,11-tetrahydroquinolino[3′,2′:4,5]thieno[2,3-e]-s-triazolo[4,3-c]pyrimiden-3 (2H) thione (**10**).

The structure of all newly synthesized compounds was confirmed on the basis of their elemental analyses and spectral data (Table II).

EXPERIMENTAL

All melting points were determined on a Kofler melting point apparatus and they are uncorrected. IR spectra were obtained using a Pye-Unicam SP3-100 infrared spectrophotometer. The ^{1}H-NMR spectra were recorded by a varian EM-390 90 MHZ spectrometer using TMS as an internal standard. The elemental analyses were carried out by elemental analyzer 240 C.

Synthesis of 7-(p-chlorophenyl)-8,9,10,11-tetrahydroquinolino-[3′,2′:4,5]thieno[2,3-e]-s-triazolo[4,3-c]-pyrimidine (**3**): Hydrazino-compound (**2**) (0.3 g) in formic acid (20 ml) was refluxed for 5 hrs. The reaction mixture was cooled and diluted with water and a white compound was precipitated. It was collected by filtration and crystallized from ethanol as colorless needles, mp. 304–5°C yield 0.25 g (83%). 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, 61.37; H, 3.62; N, 17.71; S, 8.00; Cl, 9.00%.

Synthesis of 3-methyl-7-(p-chlorophenyl)-8,9,10,11-tetrahydroquinolino-[3′,2′:4,5]thieno[2,3-e]-s-triazolo[4,3-c]pyrimidine (**4**): Hydrazino-derivative (**2**) (0.5 g) in glacial acetic acid (30 ml) was refluxed for 5 hrs. The reaction mixture was diluted with water; a white solid precipitated. It was crystallized from ethanol as white prisms mp. 320–3°C, yield 0.4 g (75%). Anal. Calcd. for $C_{21}H_{16}ClN_5S$: C, 62.14; H, 3.97; N, 17.25; S, 7.90; Cl, 8.73%. Found: C, 62.01; H, 4.06; N, 17.23; S, 8.00; Cl, 8.96%.

Synthesis of 1,2,2-triacetyl-1-(11-p-chlorophenyl-7,8,9,10-tetrahydroquinolino[3′,2′:4,5]thieno[3,2-d]pyrimidin-4-yl)hydrazine (**5**): Compound **2** (0.3 g) in redistilled acetic anhydride (20 ml) was refluxed for 4 hrs. The reaction mixture was diluted with water and the precipitate was recrystallized from ethanol

as colorless needles, mp. 195–6°C yield 0.35 g (88%). Anal. Calcd. for $C_{25}H_{22}ClN_5O_3S$: C, 59.11; H, 4.37; N, 13.79; S, 6.31; Cl, 6.98%. Found: C, 59.19; H, 4.41; N, 13.66; S, 6.50; Cl, 7.00%.

Aromatic aldehydes, (11-p-chlorophenyl-7,8,9,10-tetrahydroquinolino[3',2':4,5]thieno[3,2-d]pyrimidin-4-yl)hydrazones (**6a–c**): A mixture of the hydrazino-compound (**2**) (1.95 g, 0.005 mole) and aromatic aldehyde (0.005 mole) in 50 dioxane was refluxed for 3 hrs. On cooling, the precipitated product was collected and recrystallized from dioxane. The results are summarized in Table (I).

Synthesis of 3-aryl-7-(p-chlorophenyl)-7,8,9,10-tetrahydroquinolino-[3',2':4,5]thieno[2,3-e]-s-triazolo[4,3-c]pyrimidines (**7a–c**):

Method A:

Compound **6a–c** (0.5 g) in thionyl chloride (25 ml) was refluxed on a water bath for 2 hrs. The excess of thionyl chloride was removed by distillation under reduced pressure. The residue was triturated with water and the precipitate was crystallized from ethanol-chloroform to give (**7a–c**). The results are given in Table (I).

Method B:

A mixture of **2** (1.95 g, 0.005 mole) and benzoyl chloride (8 ml) was refluxed for 2 hrs. Excess benzoyl chloride was removed by extraction with pet ether (60–80) and the residue was crystallized from ethanol-chloroform as yellow needles of 254a, mp. 266–7°C, m.m.p. 266°C, yield 1.05 g (45%).

Synthesis of 4-(3,5-dimethylpyrazol-1-yl)-11-(p-chlorophenyl)-7,8,9,10-tetrahydroquinolino[3',2':4,5]-thieno[3,2-d]pyrimidine (**8**): The hydrazino-compound (**2**) (0.38 g, 0.001 mole) and acetylacetone (10 ml, 0.1 mole) were heated under reflux for 4 hrs. The reaction mixture was diluted with ethanol and allowed to cool whereby crystalline product precipitated. It was filtered off, washed well with ethanol and recrystallized from dimethylformamide in the form of colorless needles, mp. 233–4°C, yield 0.35 g (79%). Anal. Calcd. for $C_{24}H_{20}ClN_5S$: C, 64.64; H, 4.52; N, 15.70; S, 7.19; Cl, 7.95%. Found: C, 64.80; H, 4.50; N, 15.53; S, 7.40; Cl, 8.00%.

Synthesis of 3-ethoxycarbonylmethyl-7-(p-chlorophenyl)-8,9,10,11-tetrahydroquinolino[3',2':4,5]thieno[2,3-e]-s-triazolo[4,3-c]-pyrimidine (**9**): The hydrazino-compound (**2**) (0.38 g, 0.001 mole) was heated under reflux, with 5 ml of diethyl malonate for 6 hrs. The reaction mixture was cooled and the excess diethyl malonate was removed by extraction several times with petroleum ether (40–60). The residue was crystallized from ethanol into white needles mp. 232–3°C, yield 0.3 g (60%). Anal. Calcd. for $C_{24}H_{20}ClN_5O_2S$: C, 60.31; H, 4.22; N, 14.65; S, 6.71; Cl, 7.42%. Found: C, 60.00; H, 4.25; N, 14.82; S, 6.56; Cl, 7.45%.

Synthesis of 7-(p-chlorophenyl)-8,9,10,11-tetrahydroquinolino-[3',2':4,5]thieno[2,3-e]-s-triazolo[4,3-c]-pyrimidin-3 (2H)-thione (**10**): A mixture of the hydrazino-derivative (**2**) (0.3 g), potassium hydroxide (0.1 g) and carbon disulfide (2 ml) in iso-propanol was refluxed for 5 hrs. The reaction mixture was filtered, cooled and neutralized with cetic acid. The precipitate was collected and crystallized from ethanol as pale yellow needles mp. 290–2°C, yield 0.2 g (60%). Anal. Calcd. for $C_{20}H_{14}ClN_5S_2$: C, 56.66; H, 3.33; N, 16.52; S, 15.12; Cl, 8.36%. Found: C, 56.81; H, 3.30; N, 16.82; S, 15.00, Cl, 8.26%.

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