SYNTHESIS OF SOME NEW PYRIMIDO[4',5':4,5]THIENO[2,3-*b*]QUINOLINE DERIVATIVES

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Pyrimidine fused heterocycles have great importance in biological and medicinal chemistry. Thiazolopyrimidines for example have some analgesic activity[1]. Also, some thiopyrimidines are reported to possess effective antibacterial, antifungal, antiviral, insecticidal and miticidal activities[2 - 4]. In contrast, an exhaustive search through the Chemical Abstracts showed that only few pyrimido[4',5':4,5]thieno[2,3-*b*]quinoline derivatives have been reported[5,6]. In this paper we report the synthesis of some new pyrimidines fused with thienoquinoline moiety.

EXPERIMENTAL

All melting points are uncorrected. The IR spectra were run on a Pye–Unicam SP 3-100 spectrophotometer using KBr disc technique (wavenumbers in cm^{-1}). The ^1H NMR spectra were recorded on a Varian EM-390 90 MHz NMR spectrometer using TMS as internal standard; chemical shifts are given in ppm (δ-scale). Yields, melting points and analytical data of all reported compounds are given in Table I.

Ethyl 3-aminothieno[2,3-*b*]quinoline-2-carboxylate (*I*) was prepared according to the reported method[7].

2-Methyloxazino[4',5':4,5]thieno[2,3-*b*]quinoline-4-one (*III*)

A suspension of *I* (2.72 g, 10 mmol) in ethanolic sodium hydroxide solution (5%, 80 ml) was refluxed for 3 h. Precipitated sodium salt *II* was collected by filtration, washed with ethanol and dried in air. Sodium salt *II* (2.40 g) was refluxed for 3 h with acetic anhydride (30 ml). On cooling the crystalline product was collected and used in the next steps without further purification. A sample was recrystallized from absolute ethanol as colourless needles. ^1H NMR spectrum (CF_3CO_2D): 9.80 s, 1 H (CH-quinoline at C-11); 7.80 – 8.50 m, 4 H (aromatic); 2.60 s, 3 H (CH_3). IR spectrum: 1 740 (C=O, oxazinone); 1 600 (C=N).

3-Amino-3,4-dihydro-2-methyl-4-oxopyrimido[4',5':4,5]thieno[2,3-*b*]quinoline (*IV*)

A mixture of *II* (2.68 g, 10 mmol) and hydrazine hydrate 99% (1 ml, 20 mmol) in ethanol (60 ml) was refluxed for 3 h. The solid thus precipitated was collected and recrystallized from dioxane as colourless needles. ^1H NMR spectrum (CF_3CO_2D): 9.80 s, 1 H (CH-quinoline at C-11); 7.80 – 8.55 m, 4 H (aromatic); 2.65 s, 3 H (CH_3). IR spectrum: 3 310, 3 200 (NH_2); 1 670 (C=O); 1 600 (C=N).

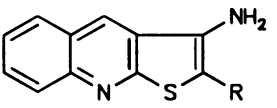
TABLE I
Yields, melting points and analytical data of the synthesized compounds

Compound	M. p., °C Yield, %	Formula (M. w.)	Calculated/Found			
			% C	% H	% N	% S
III	285 – 287 92	$C_{14}H_8N_2O_2S$ (268.3)	62.68 62.93	3.01 2.97	10.44 10.58	11.95 11.72
IV	298 – 300 65	$C_{14}H_{10}N_4OS$ (282.3)	59.56 59.72	3.57 3.55	19.85 19.68	11.36 11.50
V	252 – 255 78	$C_{18}H_{14}N_4O_3S$ (366.4)	59.01 58.88	3.85 3.98	15.29 15.19	8.75 8.70
VI	>300 90	$C_{14}H_9N_3OS$ (267.3)	62.91 62.68	3.39 3.35	15.72 15.42	11.99 12.10
VII	218 – 220 87	$C_{14}H_8ClN_3S$ (285.8)	58.85 58.77	2.82 2.85	14.71 14.81	11.22 11.00
VIII	190 – 193 69	$C_{15}H_{11}N_3OS$ (281.3)	64.04 64.50	3.94 4.08	14.94 14.70	11.40 11.50
IX	>300 95	$C_{14}H_9N_3S_2$ (283.4)	59.34 59.04	3.20 3.25	14.83 14.93	22.63 22.75
X	193 – 195 81	$C_{16}H_{13}N_3S_2$ (311.4)	61.71 61.87	4.21 4.20	13.49 13.63	20.59 20.80
XI	202 – 205 79	$C_{22}H_{15}N_3OS_2$ (401.5)	65.81 65.71	3.77 3.65	10.47 10.70	15.97 15.86
XII	135 – 137 73	$C_{19}H_{18}N_4S$ (334.4)	68.24 68.11	5.42 5.40	16.75 16.93	9.59 9.81
XIII	297 – 299 90	$C_{14}H_{11}N_5S$ (281.3)	59.77 59.94	3.94 3.93	24.89 24.80	11.40 11.52
XIV	249 – 251 80[a] 73[b]	$C_{14}H_8N_6S$ (292.3)	57.52 57.60	2.76 2.88	28.75 28.63	10.97 10.85
XV	>300 91	$C_{15}H_9N_5S$ (291.3)	61.84 61.79	3.11 3.17	24.04 24.32	11.00 11.00
XVI	225 – 227 82	$C_{20}H_{17}N_5O_3S$ (407.4)	58.96 59.17	4.21 4.20	17.19 17.53	7.87 7.95
XVII	238 – 240 60	$C_{19}H_{15}N_5S$ (345.4)	66.07 66.41	4.38 4.35	20.27 20.20	9.28 9.56
XVIII	>300 87	$C_{21}H_{15}N_5S$ (369.4)	68.27 68.03	4.09 4.06	18.96 19.11	8.68 8.80

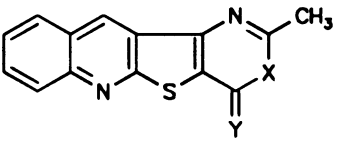
[a] Method *A*); [b] Method *B*).

Reaction of 3-Amino-3,4-dihydro-2-methyl-4-oxopyrimido[4',5':4,5]thieno[2,3-*b*]quinoline (*IV*) with Acetic Anhydride

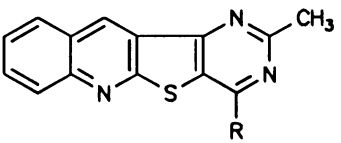
Compound *IV* (2.82 g, 10 mmol) in acetic anhydride (20 ml) was refluxed for 3 h. The reaction mixture was diluted with water whereby a yellowish white solid was precipitated. It was collected and crystallized from ethanol in the form of needle crystals. This product was identified as 3-diacetylamino-3,4-dihydro-2-methyl-4-oxopyrimido[4',5':4,5]thieno[2,3-*b*]quinoline (*V*). ^{1}H NMR spectrum ($CDCl_3$): 8.80 s, 1 H (CH-quinoline at C-11); 7.30 – 8.05 m, 4 H (aromatic); 2.45 s, 3 H (CH_3); 2.30 s, 6 H (2 × $COCH_3$). IR spectrum: 1 740 (C=O, acetyl groups); 1 690 (C=O, pyrimidinone).



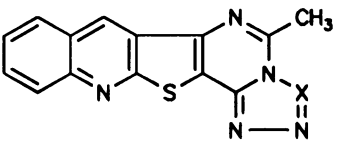
I, R = $CO_2C_2H_5$
II, R = CO_2Na



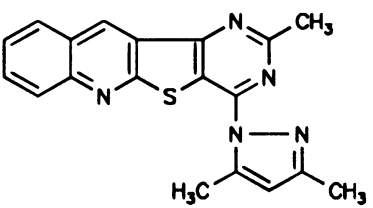
III, X = O; Y = O
IV, X = NNH_2; Y = O
V, X = $NN(COCH_3)_2$; Y = O
VI, X = NH; Y = O
IX, X = NH; Y = S



VII, R = Cl
VIII, R = OCH_3
X, R = SC_2H_5
XI, R = SCH_2COPh
XII, R = 1-piperidinyl
XIII, R = $NHNH_2$
XVI, R = $N(COCH_3)N(COCH_3)_2$
XVIII, R = NH–N=CHPh



XIV, X = N
XV, X = CH



XVII

3,4-Dihydro-2-methyl-4-oxopyrimido[4',5':4,5]thieno[2,3-*b*]quinoline (*VI*)

A mixture of *III* (2.68 g, 10 mmol) and ammonium acetate (1.54 g, 20 mmol) in glacial acetic acid (50 ml) was refluxed for 2 h. The precipitate obtained after cooling was collected and recrystallized from dioxane as white needles. ^{1}H NMR spectrum (CF_3CO_2D): 9.80 s, 1 H (CH-quinoline at C-11); 7.90 – 8.60 m, 4 H (aromatic); 3.10 s, 3 H (CH_3).

4-Chloro-2-methylpyrimido[4',5':4,5]thieno[2,3-*b*]quinoline (*VII*)

Compound *VI* (2.67 g, 10 mmol) in phosphorus oxychloride (40 ml) was refluxed for 4 h. The cooled reaction mixture was poured with vigorous stirring into ice-cold water. The white solid thus obtained was crystallized from ethanol as colourless needles. ^{1}H NMR spectrum ($CDCl_3$): 9.00 s, 1 H (CH-quinoline at C-11); 7.40 – 8.15 m, 4 H (aromatic); 2.40 s, 3 H (CH_3). IR spectrum: 1 600 (C=N).

4-Methoxy-2-methylpyrimido[4',5':4,5]thieno[2,3-*b*]quinoline (*VIII*)

A suspension of *VII* (0.29 g, 1 mmol) in 20 ml of methanol containing 0.046 g (2 mmol) sodium was refluxed for 3 h. The cooled reaction mixture was diluted with water and the product thus obtained was crystallized from ethanol as white crystals. ^{1}H NMR spectrum ($CDCl_3$): 8.80 s, 1 H (CH-quinoline at C-11); 7.30 – 8.05 m, 4 H (aromatic); 3.50 s, 3 H (OCH_3); 2.40 s, 3 H (CH_3). IR spectrum: 1 600 (C=N).

3,4-Dihydro-2-methyl-4-thioxopyrimido[4',5':4,5]thieno[2,3-*b*]quinoline (*IX*)

A mixture of *VIII* (1.43 g, 5 mmol) and thiourea (0.76 g, 10 mmol) in ethanol (40 ml) was refluxed for 4 h. On cooling, the yellow product thus precipitated was collected by filtration, dissolved in sodium carbonate solution and filtered. The clear filtrate was acidified with acetic acid and the solid obtained was crystallized from dioxane as orange crystals. ^{1}H NMR spectrum (CF_3CO_2D): 9.80 s, 1 H (CH-quinoline at C-11); 7.90 – 8.65 m, 4 H (aromatic); 3.25 s, 3 H (CH_3). IR spectrum: 3 160 (NH).

Alkylation of *IX*; Formation of *X* and *XI*

A mixture of *IX* (0.85 g, 3 mmol) and the respective alkylating agent (4 mmol) in pyridine (20 ml) was heated under reflux for 2 h. The reaction mixture was cooled and diluted with water (30 ml). The solid thus formed was collected and crystallized from ethanol. In this way, the following compounds were prepared:

4-Ethylthio-2-methylpyrimido[4',5':4,5]thieno[2,3-b]quinoline (X): Obtained from *IX* and ethyl iodide as white needles. ^{1}H NMR spectrum (CF_3CO_2D): 9.80 s, 1 H (CH-quinoline at C-11); 7.90 – 8.60 m, 4 H (aromatic); 3.50 – 3.80 q, 2 H (SCH_2); 3.15 s, 3 H (CH_3); 1.40 – 1.70 t, (CH_3). IR spectrum: 1 600 (C=N).

2-Methyl-4-phenacylthiopyrimido[4',5':4,5]thieno[2,3-b]quinoline (XI): Obtained from *IX* and phenacyl bromide as yellow prisms. ^{1}H NMR spectrum ($CDCl_3$): 8.90 s, 1 H (CH-quinoline at C-11); 7.50 – 8.30 m, 9 H (aromatic); 4.80 s, 2 H (SCH_2); 2.40 s, 3 H (CH_3). IR spectrum: 1 680 (C=O); 1 600 (C=N).

2-Methyl-4-(N-piperidinyl)pyrimido[4',5':4,5]thieno[2,3-*b*]quinoline (*XII*)

A mixture of *VII* (1.46 g, 5 mmol) and piperidine (3 ml) was refluxed for 4 h. Excess piperidine was removed in vacuum and the residual solid was washed with water and crystallized from methanol as colourless plates. ^{1}H NMR spectrum ($CDCl_3$): 8.90 s, 1 H (CH-quinoline at C-11); 7.30 – 8.20 m, 4 H (aromatic); 3.75 – 4.00 t, 4 H (two methylene groups of piperidine ring); 2.45 s, 3 H (CH_3); 1.30 – 1.60 m, 6 H (three methylene groups of piperidine ring). IR spectrum: 2 940 (CH, aliphatic); 1 600 (C=N).

4-Hydrazino-2-methylpyrimido[4',5':4,5]thieno[2,3-*b*]quinoline (*XIII*)

A mixture of *VII* (2.85 g, 10 mmol) and hydrazine hydrate 99% (2 ml, 20 mmol) in ethanol (40 ml) was refluxed for 2 h. The precipitated product was filtered off and recrystallized from dioxane as yellow crystals. ^{1}H NMR spectrum: 9.90 s, 1 H (CH-quinoline at C-11); 8.00 – 8.70 m, 4 H (aromatic); 3.25 s, 3 H (CH_3). IR spectrum: 3 370, 3 200 ($NHNH_2$); 1 630, 1 610 (C=N).

5-Methyltetrazolo[4",3":1',6']pyrimido[4',5':4,5]thieno[2,3-*b*]quinoline (*XIV*)

Method *A*): To a cold solution of *XIII* (2.81 g, 10 mmol) in concentrated hydrochloric acid (5 ml) and glacial acetic acid (5 ml) at 0 °C, a solution of sodium nitrite (7 ml, 10%; 10 mmol) was added. The product obtained was crystallized from ethanol as white needles. ^{1}H NMR spectrum ($CDCl_3$): 8.80 s, 1 H (CH-quinoline at C-11); 7.30 – 8.05 m, 4 H (aromatic); 2.40 s, 3 H (CH_3). IR spectrum: 1 620, 1 600 (C=N).

Method *B*): A mixture of *VII* (0.29 g, 1 mmol) and sodium azide (0.26 g, 4 mmol) in glacial acetic acid (20 ml) was refluxed for 4 h. The reaction mixture was diluted with water. The product obtained upon crystallization was identical to that reported in Method *A*) according to melting point and spectral data.

5-Methyl-5-triazolo[4",3":1',6']pyrimido[4',5':4,5]thieno[2,3-*b*]quinoline (*XV*)

A mixture of *XIII* (1.40 g, 5 mmol), triethyl orthoformate (1.48 g, 10 mmol) and acetic anhydride (20 ml) was refluxed for 3 h. The crystalline solid thus obtained was recrystallized from dioxane in the form of fine needles. ^{1}H NMR spectrum (CF_3CO_2D): 10.00 s, 1 H (CH); 9.70 s, 1 H (CH); 8.00 – 8.80 m, 4 H (aromatic); 3.20 s, 3 H (CH_3). IR spectrum: 1 610, 1 590 (C=N).

Reaction of 4-Hydrazino-2-methylpyrimido[4',5':4,5]thieno[2,3-*b*]quinoline (*XIII*) with Acetic Anhydride

Compound *XIII* (2.81 g, 10 mmol) in acetic anhydride (20 ml) was refluxed for 3 h. The reaction mixture was concentrated and diluted with water whereby a white solid was obtained. It was crystallized from ethanol as yellowish white prisms. This product was identified as 2-methyl-4-(1,2,2-triacetylhydrazino)pyrimido[4',5':4,5]thieno[2,3-*b*]quinoline (*XVI*). ^{1}H NMR spectrum (CF_3CO_2D): 10.20 s, 1 H (CH-quinoline at C-11); 8.10 – 8.70 m, 4 H (aromatic); 3.20 s, 3 H (CH_3); 2.65 s, 9 H (3 × $COCH_3$). IR spectrum: 1 730, 1 660 (C=O); 1 600 (C=N).

4-(2',5'-Dimethylpyrazol-1'-yl)-2-methylpyrimido[4',5':4,5]thieno[2,3-*b*]quinoline (*XVII*)

A mixture of acetylacetone (1.0 g, 10 mmol) and *XIII* (2.81 g, 10 mmol) was refluxed in methanol (40 ml) containing 4 to 5 drops of hydrochloric acid for 3 h. The solid which separated on cooling and basification with ammonia solution, was collected and crystallized from ethanol as yellow crystals. ^{1}H NMR spectrum (CF_3CO_2D): 10.20 s, 1 H (CH-quinoline at C-11); 7.20 s, 1 H (CH-pyrazole); 3.20 s, 3 H (CH_3); 2.90 s, 3 H (CH_3-attached to pyrazole ring); 2.50 s, 3 H (CH_3-attached to pyrazole ring). IR spectrum: 1 600 (C=N).

N^1-Benzylidene(2-methylpyrimido[4',5':4,5]thieno[2,3-*b*]quinoline-4-yl) Hydrazine (*XVIII*)

A mixture of *XIII* (1.40 g, 5 mmol) and benzaldehyde (0.53 g, 5 mmol) in dioxane (30 ml) was refluxed for 2 h. On cooling, the precipitated solid was collected and recrystallized from dioxane as yellow needles. ^{1}H NMR spectrum (CF_3CO_2D): 9.90 s, 1 H (CH-quinoline); 7.50 – 8.70 m, 10 H (9 H, aromatic and 1 H, CH=N) and 3.00 s, 3 H (CH_3). IR spectrum: 3 200 (NH); 1 610, 1 590 (C=N).

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