

SYNTHESIS AND REACTIONS OF SOME NEW 3-AMINO-2-SUBSTITUTED THIENO[2,3-*b*]QUINOLINES

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Reaction of 3-cyano-quinolin-2(1*H*)-thione (*II*) with ω -bromoacetophenones gave 3-amino-2-arylthieno[2,3-*b*]quinolines (*IVa* – *IVd*). Whereas, interaction of *II* with chloroacetanilides yielded the corresponding thioethers *Va* – *Vc* which cyclized into 3-amino-2-arylcarbamoylthieno[2,3-*b*]quinolines (*VIa* – *VIc*) on treatment with ethoxide. Compounds *VIa* – *VIc* were reacted with nitrous acid, triethyl orthoformate and carbon disulfide to afford the fused polycyclic compounds *VIIa* – *VIIc*, *VIIIa* – *VIIIc*, and *IXa* – *IXc*, respectively. Also, treatment of *IXa* – *IXc* with ethyl iodide gave 3-ethylthio derivatives *Xa* – *Xc*. Moreover, refluxing of *VIa* – *VIc* with acetic anhydride resulted in the formation of oxazinone *XI* which cyclized into pyrimidinones *XIIIa* – *XIIIc* upon reaction with aromatic amines.

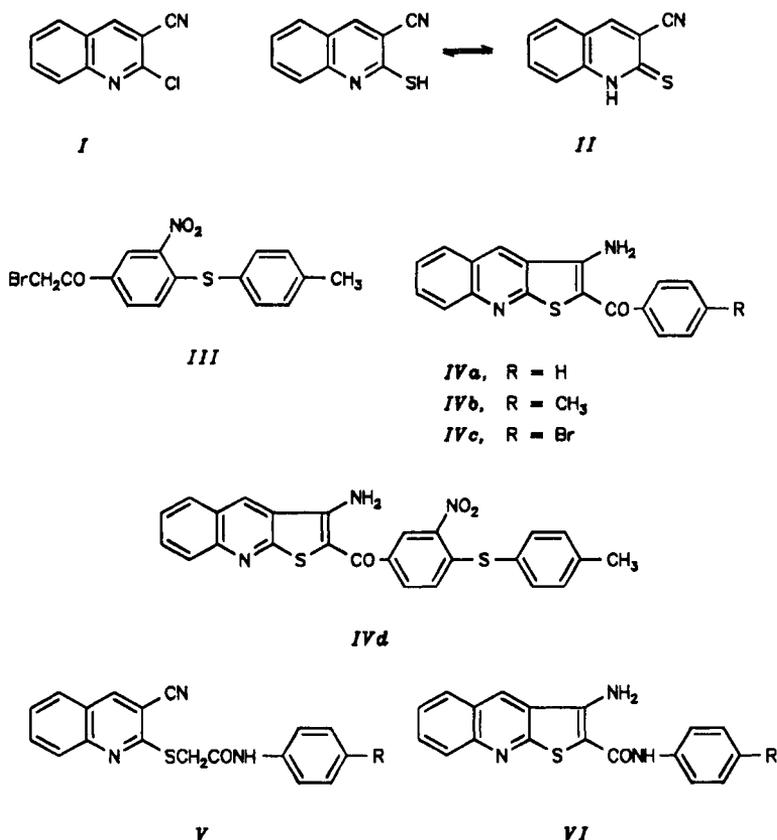
In continuation of our previous work on thieno[2,3-*b*]quinolines¹⁻³, we describe in this paper the synthesis of some new thieno[2,3-*b*]quinolines and their reactions with different reagents.

The starting compound *II* was obtained in 95% yield by reaction of 2-chloro-quinoline-3-carbonitrile (*I*) with thiourea in refluxing methanol. Reaction of *II* with phenacyl bromide and its derivatives in refluxing ethanol containing triethyl amine gave 3-amino-2-arylthieno[2,3-*b*]quinolines (*IVa* – *IVc*). Similarly, compound *II* was reacted with 3-nitro-4-tolylthio-phenacyl bromide (*III*) to afford the corresponding thienoquinoline derivative *IVd* in high yield.

Whereas, reaction of *II* with chloroacetanilide and its derivatives by refluxing in ethanol containing sodium acetate gave 2-arylcarbamoylmethylthioquinoline-3-carbonitriles (*Va* – *Vc*). On treatment of *Va* – *Vc* with sodium ethoxide in ethanol, the corresponding thienoquinoline derivatives *VIa* – *VIc* were obtained in nearly quantitative yields. The latter compounds (*VIa* – *VIc*) were also synthesized by one step reaction from *II* and chloroacetanilides in the presence of sodium ethoxide.

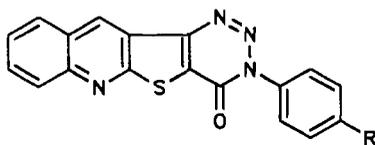
Diazotization of *VIa* – *VIc* with sodium nitrite – hydrochloric acid in acetic acid furnished 3-aryl-3,4-dihydro-4-oxo-1,2,3-triazino[4',5':4,5]thieno[2,3-*b*]quinolines (*VIIa* – *VIIc*). In contrast, the pyrimidine analogues *VIIIa* – *VIIIc* were obtained smoothly by condensation of *VIa* – *VIc* with triethyl orthoformate in refluxing acetic anhydride. Also, interaction of *VIa* – *VIc* with carbon disulfide in pyridine led to the

formation of 3-aryl-4-oxo-1,2,3,4-tetrahydro-2-thioxopyrimido[4',5':4,5]thieno[2,3-*b*]quinolines (*IXa - IXc*). Compounds *IXa - IXc* were S-ethylated by ethyl iodide in ethanolic sodium hydroxide solution to give 2-ethylthiopyrimidinone derivatives *Xa - Xc* in good yields. Moreover, heating of *VIa - VIc* with acetic anhydride at refluxing temperature does not give the expected pyrimidinones *XIIIa - XIIIc* and instead of, a mixture of oxazinone *XI* and the corresponding acetanilides *XII* was obtained. Oxazinone *XI* underwent ring transformation into 3-aryl-2-methyl-3,4-dihydro-4-oxopyrimido[4',5':4,5]thieno[2,3-*b*]quinolines (*XIIIa - XIIIc*) upon treatment with the appropriate aromatic amine.

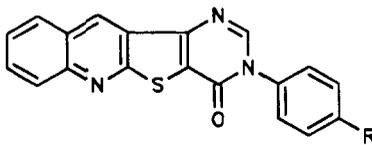


In formulae *V* and *VI* : *a*, R = H; *b*, R = OCH₃; *c*, R = Cl

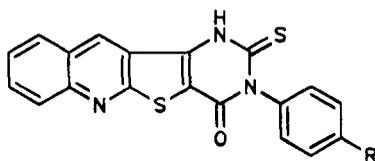
The structures of all newly synthesized compounds were confirmed on the basis of their elemental analyses (Table I), IR and ^1H NMR spectra.



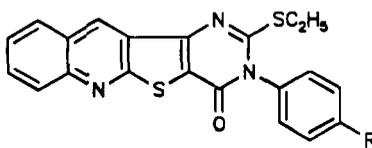
VII



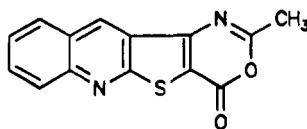
VIII



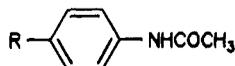
IX



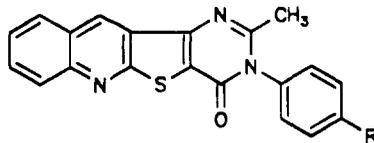
X



XI



XII



XIII

In formulae VII-X, XII, and XIII : a, R = H; b, R = OCH₃; c, R = Cl

EXPERIMENTAL

All melting points are uncorrected. The IR spectra were measured 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 ^1H 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.

3-Cyano-quinolin-2(1H)-thione (II)

A mixture of I (ref.⁴, 1.5 g, 8 mmol) and thiourea (0.76 g, 10 mmol), in dry methanol (25 ml) was heated under reflux for 3 h. The separated yellow crystalline solid was collected, washed with ethanol and heated with aqueous sodium hydroxide 10% (15 ml) at 80 °C for 15 min. On cooling and acidification, the quinolinethione (II) was obtained as a yellow powder and was crystallized from N,N-dimethylformamide-water as yellow needles. ^1H NMR spectrum (CD_3SOCD_3): 14.10 (s, 1H, NH); 8.64 (s, 1H, CH-quinoline at C-4); 7.20 – 8.00 (m, 4H, aromatic). IR spectrum: 3 100 (NH), 2 230 (C=N), 1 230 (C=S).

3-Amino-2-aryl-thieno[2,3-b]quinolines IVa – IVc

A mixture of II (1.86 g, 10 mmol) and the appropriate ω -bromoacetophenone (10 mmol) in ethanol (30 ml), triethylamine (2 ml) was added. The mixture was refluxed for 2 h. The red precipitate thus formed was collected and recrystallized from ethanol-chloroform mixture as fine red plates. IR spectra of IVa – IVc showed characteristic absorption bands at 3 340, 3 240 for (NH_2) and at 1 620 for (C=O).

3-Amino-2-[3-nitro-4-(*p*-tolylthio)benzoyl]thieno[2,3-b]quinoline IVd

This compound was synthesized in analogy to the method described above by reaction of II and 3-nitro-4-(*p*-tolylthio)phenacyl bromide⁵ (III). The product was recrystallized from ethanol as orange crystals. ^1H NMR spectrum (CD_3SOCD_3): 9.30 (s, 1H, CH-quinoline); 7.30 – 8.80 (m, 11H, aromatic); 6.80 (s, 2H, NH_2); 2.30 (s, 3H, CH_3). IR spectrum: 3 340, 3 240 (NH_2); 1 620 (C=O).

2-Arylcabamoylmethylthioquinoline-3-carbonitriles Va – Vc

To a suspension of II (1.86 g, 10 mmol) and anhydrous sodium acetate (1.25 g, 15 mmol) in ethanol (30 ml), the appropriate chloroacetanilide (10 mmol) was added. The reaction mixture was refluxed for 2 h. On cooling, the precipitate was collected and recrystallized from ethanol in the form of white needles.

Compound Va. ^1H NMR spectrum (CDCl_3): 9.90 (s, 1H, CONH and exchangeable with D_2O); 8.90 (s, 1H, CH at C-4); 7.20 – 8.20 (m, 9H, aromatic); 4.40 (s, 2H, SCH_2). The IR spectra of compounds Va – Vc showed characteristic absorption bands at 3 300 – 3 250 for (NH), at 2 210 for (C=N) and at 1 680 – 1 670 for (C=O).

3-Amino-2-arylcabamoyl-thieno[2,3-b]quinolines VIa – VIc

A) Compounds Va – Vc (10 mmol) in ethanol (40 ml) containing dissolved sodium (10 mg) were refluxed for 10 min. The solids obtained after cooling were recrystallized from ethanol-chloroform mixture as golden yellow prisms of VIa – VIc. The IR spectra of VIa – VIc exhibit characteristic bands at 3 400, 3 300 for (NH_2); at 3 190 (NH) and at 1 620 for (C=O).

B) A mixture of II (1.86 g, 10 mmol) and the respective chloroacetanilide (10 mmol) in sodium ethoxide solution (500 mg sodium in 50 ml ethanol) was refluxed for 1 h. The solids obtained upon recrystallized were identical to those described in method A).

3-Aryl-3,4-dihydro-4-oxo-1,2,3-triazino[4',5':4,5]thieno[2,3-*b*]quinolines *VIIa* – *VIIc*

To a solution of *Via* – *Vtc* (9 mmol) in concentrated hydrochloric acid (5 ml) and glacial acetic acid (5 ml) was added 10% sodium nitrite solution (7 ml, 10 mmol) at 0 °C during 5 min with stirring. The white product thus formed was collected and crystallized from chloroform as fine white needles. The IR spectra of *VIIa* – *VIIc* showed absorption band at 1 690 characteristic for (C=O, triazinone).

3-Aryl-3,4-dihydro-4-oxopyrimido[4',5':4,5]thieno[2,3-*b*]quinolines *VIIIa* – *VIIIc*

A mixture of *Via* – *Vtc* (10 mmol) and triethyl orthoformate (2 ml, 12 mmol) in acetic anhydride (20 ml) was refluxed for 4 h. The crystalline solid thus formed was collected and recrystallized from ethanol as white needles.

Compound VIIIc. ¹H NMR spectrum (CDCl₃): 9.80 (s, 1H, CH-pyrimidinone); 8.70 (s, 1H, CH-quinoline at C-11); multiplet at 7.20 – 8.60 (8H, aromatic). The IR spectra of compounds *VIIIa* – *VIIIc* showed absorption band at 1 670 characteristic for (C=O, pyrimidinone).

3-Aryl-4-oxo-1,2,3,4-tetrahydro-2-thioxopyrimido[4',5':4,5]thieno[2,3-*b*]quinolines *IXa* – *IXc*

A mixture of *Via* – *Vtc* (5 mmol) and carbon disulfide (4 ml, 66.5 mmol) in dry pyridine (30 ml) was heated on a water bath for 8 h; during the reaction time hydrogen sulfide was evolved. The solvent was distilled off in vacuum and the residue was crystallized from pyridine as fine yellow needles of *IXa* – *IXc*. The IR spectra of these compounds exhibit characteristic absorption bands at 3 100 for (NH) and at 1 680 for (C=O).

3-Aryl-2-ethylthio-3,4-dihydro-4-oxopyrimido[4',5':4,5]thieno[2,3-*b*]quinolines *Xa* – *Xc*

Compound *IXa* – *IXc* (4 mmol) was dissolved in ethanolic sodium hydroxide solution 4% (20 ml). To this solution ethyl iodide (0.4 ml, 5 mmol) was added and the resulting mixture was refluxed for 1 h. On cooling and dilution with water, the solid formed was collected and crystallized from ethanol as pale yellow needles.

Compound Xb. ¹H NMR spectrum (CDCl₃): 9.40 (s, 1H-quinoline at C-11); 7.80 – 8.40 (s, 4H, aromatic protons of quinoline nucleus); 6.90 – 7.30 (dd, 4H, aromatic); 3.80 (s, 3H, OCH₃); 3.20 – 3.40 (q, 2H, CH₂); 1.30 – 1.50 (t, 3H, CH₃). The IR spectra of compounds *Xa* – *Xc* revealed the presence of absorption band at 1 670 characteristic for (C=O, pyrimidinone).

Reaction of 3-Amino-2-arylcabamoylthieno[2,3-*b*]quinolines *VIa* – *VIc* with Acetic Anhydride

A mixture of *VIa* – *VIc* (10 mmol) and acetic anhydride (50 ml) was refluxed for 4 h. The reaction mixture was concentrated and allowed to cool. The product precipitated was filtered off and recrystallized from ethanol as white needles. This product was identified as 2-methyl-4-oxo-oxazino[4',5':4,5]thieno[2,3-*b*]quinoline (*XI*). ¹H NMR spectrum (CDCl₃): 8.30 (s, 1H, CH-quinoline at C-11); 7.30 – 7.90 (m, 4H, aromatic); 2.10 (s, 3H, CH₃). IR spectrum showed absorption band at 1 740 characteristic for (C=O, lactone).

The filtrate from the above crude product was diluted with water whereby a white solid was precipitated which upon purification assigned as the corresponding acetanilide *XIIa* – *XIIc*.

3-Aryl-2-methyl-3,4-dihydro-4-oxopyrimido[4',5':4,5]thieno[2,3-*b*]quinolines *XIIIa* – *XIIIc*

A mixture of oxazinone *XI* (1.43 g, 5 mmol) and the respective aromatic amine (5 mmol) in glacial acetic acid (20 ml) was refluxed for 4 h. The reaction mixture was cooled and diluted with water whereby a white solid precipitated. It was filtered off and crystallized from ethanol as white needles.

Compound XIIIb. ^1H NMR (CDCl_3): 8.90 (s, 1H, CH-quinoline); 6.90 – 8.20 (m, 8H aromatic); 3.80 (s, 3H, OCH_3); 2.30 (s, 3H, CH_3). The IR spectra of compounds XIIIa – XIIIc exhibited characteristic absorption band at 1 680 for ($\text{C}=\text{O}$, pyrimidinone).

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	% Cl
II	>300 ^a	95	$\text{C}_{10}\text{H}_6\text{N}_2\text{S}$ (186.2)	64.50	3.25	15.04	17.22	–
				64.63	3.10	15.00	17.30	–
IVa	250 – 251	79	$\text{C}_{18}\text{H}_{12}\text{N}_2\text{OS}$ (304.4)	71.03	3.97	9.20	10.53	–
				70.88	3.94	9.27	10.83	–
IVb	275 – 277	80	$\text{C}_{19}\text{H}_{14}\text{N}_2\text{OS}$ (318.4)	71.68	4.43	8.80	10.07	–
				71.50	4.49	8.92	10.00	–
IVc	340 – 342	86	$\text{C}_{18}\text{H}_{11}\text{BrN}_2\text{OS}$ (383.3)	56.41	2.89	7.31	8.37	– ^b
				56.75	2.91	7.30	8.50	– ^b
IVd	195 – 198	73	$\text{C}_{25}\text{H}_{17}\text{N}_3\text{O}_3\text{S}_2$ (471.5)	63.68	3.63	8.91	13.60	–
				63.53	3.70	9.16	13.36	–
Va	225 – 226	87	$\text{C}_{18}\text{H}_{13}\text{N}_3\text{OS}$ (319.4)	67.69	4.10	13.16	10.04	–
				67.64	4.28	13.13	10.00	–
Vb	>300	90	$\text{C}_{19}\text{H}_{15}\text{N}_3\text{O}_2\text{S}$ (349.4)	65.31	4.33	12.03	9.18	–
				65.49	4.58	11.98	9.25	–
Vc	233 – 234	84	$\text{C}_{18}\text{H}_{12}\text{ClN}_3\text{OS}$ (353.8)	61.10	3.42	11.88	9.06	–
				61.35	3.41	11.72	9.00	–
VIa	266 – 268	95 ^c	$\text{C}_{18}\text{H}_{13}\text{N}_3\text{OS}$ (319.4)	67.69	4.10	13.16	10.04	–
		79 ^d		67.45	4.15	12.97	10.30	–
VIb	245 – 246	97 ^c	$\text{C}_{19}\text{H}_{15}\text{N}_3\text{O}_2\text{S}$ (349.4)	65.31	4.33	12.03	9.18	–
		78 ^d		65.01	4.46	11.79	9.06	–
VIc	288 – 290	94 ^c	$\text{C}_{18}\text{H}_{12}\text{ClN}_3\text{OS}$ (353.8)	61.10	3.42	11.88	9.06	10.02
		80 ^d		61.19	3.40	12.07	9.00	9.70
VIIa	290 – 291	81	$\text{C}_{18}\text{H}_{10}\text{N}_4\text{OS}$ (330.4)	65.44	3.05	16.96	9.70	–
				65.62	3.03	16.82	9.50	–
VIIb	295 – 297	78	$\text{C}_{19}\text{H}_{12}\text{N}_4\text{O}_2\text{S}$ (360.4)	63.32	3.36	15.55	8.90	–
				63.00	3.27	15.38	9.00	–
VIIc	>300	76	$\text{C}_{18}\text{H}_9\text{ClN}_4\text{OS}$ (364.8)	59.26	2.49	15.36	8.79	9.72
				59.29	2.46	15.15	8.70	10.00

TABLE I
(Continued)

Compound	M. p., °C	Yield, %	Formula (M. w.)	Calculated / Found				
				% C	% H	% N	% S	% Cl
<i>VIIIa</i>	290 – 292	82	C ₁₉ H ₁₂ N ₃ OS (329.4)	69.29	3.37	12.76	9.73	–
				69.51	3.30	12.73	9.60	–
<i>VIIIb</i>	>300	89	C ₂₀ H ₁₃ N ₃ O ₂ S (359.4)	66.84	3.65	11.69	8.92	–
				67.03	3.65	11.82	8.90	–
<i>VIIIc</i>	>300	85	C ₁₉ H ₁₀ ClN ₃ OS (363.8)	62.73	2.77	11.55	8.81	9.74
				62.55	2.69	11.63	9.00	10.00
<i>IXa</i>	>300	76	C ₁₉ H ₁₁ N ₃ OS ₂ (361.4)	63.14	3.07	11.63	17.74	–
				63.28	3.05	11.70	17.62	–
<i>IXb</i>	>300	73	C ₂₀ H ₁₃ N ₃ O ₂ S ₂ (391.5)	61.37	3.35	10.73	16.38	–
				61.45	3.31	10.89	16.20	–
<i>IXc</i>	>300	77	C ₁₉ H ₁₀ ClN ₃ OS ₂ (395.9)	57.65	2.55	10.61	16.20	8.96
				57.50	2.56	10.50	16.10	9.06
<i>Xa</i>	238 – 239	80	C ₂₁ H ₁₅ N ₃ OS ₂ (389.5)	64.76	3.88	10.79	16.46	–
				64.82	3.84	10.63	16.50	–
<i>Xb</i>	266 – 267	82	C ₂₂ H ₁₇ N ₃ O ₂ S ₂ (419.5)	62.99	4.08	10.02	15.28	–
				62.87	4.06	10.31	15.35	–
<i>Xc</i>	>300	80	C ₂₁ H ₁₅ ClN ₃ OS ₂ (423.9)	59.50	3.33	9.91	15.13	8.36
				60.00	3.39	9.85	15.00	8.50
<i>XI</i>	277 – 280	80 – 85 ^e	C ₁₄ H ₈ N ₂ O ₂ S (268.3)	62.68	3.01	10.44	11.95	–
				62.91	3.00	10.35	12.07	–
<i>XIIIa</i>	284 – 286	81	C ₂₀ H ₁₃ N ₃ OS (343.4)	69.95	3.82	12.24	9.34	–
				69.76	3.81	12.40	9.30	–
<i>XIIIb</i>	267 – 268	80	C ₂₁ H ₁₅ N ₃ O ₂ S (373.4)	67.55	4.05	11.25	8.59	–
				67.83	4.09	11.21	9.00	–
<i>XIIIc</i>	282 – 284	83	C ₂₀ H ₁₂ ClN ₃ OS (377.8)	63.58	3.20	11.12	8.49	9.38
				63.41	3.15	11.00	8.24	9.50

^a Literature⁶ gives m.p. 290 °C. ^b Calculated: 20.85% Br; found: 21.00% Br. ^c Yields of method A).

^d Yields of method B). ^e Yield ranged from 80% to 85%.

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