Thienoquinolines Part 1. Synthesis of Thieno[2,3-*b*]quinolines

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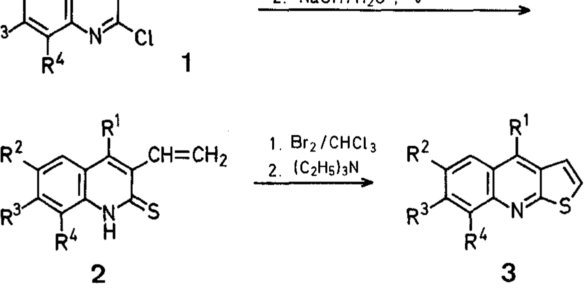
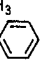
The furo[2,3-*b*]quinoline ring system has been constructed by a wide variety of methods reported[1] in literature. But, for the corresponding thieno-analogue (3, $R^1 = R^2 = R^3 = R^4 =$ H), only three methods have hitherto been recorded[2,3,4]. Of them, the one due to Hull[2] involves ring-scission of quinoline with thiophosgene as the starting point. Kuwayama and coworkers[3] described the preparation of the parent compound as a result of a five-stage process from 3-(2-hydroxyethyl)-quinolin-2(1*H*)-one. Jen and coworkers[4] obtained the dihydro derivative of the parent thienoquinoline starting from 2-nitrobenzylidene-γ-butyrolactone.

The most direct and versatile route to the thieno[2,3-*b*]quinoline system appears to be via quinolin-2(1*H*)-thione possessing a vinyl functionality at C-3-position. In this communication we wish to report a facile and convenient synthesis of thieno[2,3-*b*]quinolines achieved through the use of appropriately substituted 3-vinylquinolin-2(1*H*)-thiones.



	R^1	R^2	R^3	R^4
a	CH_3	H	H	H
b	CH_3	H	OCH_3	H
c	CH_3	OCH_3	OCH_3	H
d	CH_3	H	OCH_3	OCH_3
e	CH_3	H	CH_3	H
f	CH_3	H	Cl	H
g		H	H	H
h		H	H	H

The chloroquinolines **1a–h** were obtained from the respective 3-vinylquinolin-2(1*H*)-ones by treatment with phosphoryl chloride and were converted into the corresponding quinolinethiones **2a–h** by reaction with thiourea in boiling ethanol followed by treatment of the resultant product with aqueous alkali. The vinyl compounds **2a–h** were transformed into the corresponding thieno[2,3-*b*]quinolines **3a–h** by a bromine addition-dehydrobromination sequence as an one-pot reaction. Addition of bromine to the vinyl compound in chloroform solution and heating the reaction mixture with triethylamine at reflux readily furnished the corresponding thieno[2,3-*b*]quinoline. The intermediate bromine-addition product need not be isolated, although it has been done so in the case of **2a**. The I.R. spectrum of the bromine adduct showed the absence of the band due to the vinyl group as expected.

The structures of the thienoquinolines (**3a–h**) as well as of the chloroquinolines (**1a–h**) were fully attested by their ^{1}H-N.M.R. spectra. The N.M.R. spectra of the quinolinethiones (**2a–g**) could not be obtained because of their poor solubility in usual spectral solvents.

The above synthetic procedure, by virtue of its simplicity and apparent generality may be considered as a valuable addition to the previously reported routes[2,3,4] for the construction of thieno[2,3-*b*]quinoline ring system.

Interestingly, attempts to prepare **2a** from 4-methyl-3-vinylquinolin-2(1*H*)-one by heating with tetraphosphorus decasulfide in pyridine afforded, in addition to **2a** (20% yield), the 2,3-dihydro derivative of **3a** (10% yield).

Melting points were determined on a Boetius microheating table and are uncorrected. The N.M.R. spectra were determined on a Varian-A 60 spectrometer (TMS internal standard) and I.R. spectra on a Perkin-Elmer Model 337 spectrometer.

2-Chloro-4-methyl-3-vinylquinoline (1a):
4-Methyl-3-vinylquinolin-2(1*H*)-one[1c] (1.87 g, 10 mmol) was heated with freshly distilled phosphoryl chloride (4 ml) on a steam-bath for 2 h. On cooling and pouring into crushed ice the chloroquinoline slowly separated as a creamy white solid. It was collected, washed, dried, and chromatographed over alumina with benzene/hexane (1 : 1) as eluent, when **1a** was obtained as colourless needles. (For m.p., yield, etc. see Table 1).

A similar procedure was adopted for the preparation of **1b–h**. Use of 7-methoxy-4-methyl-[1c], 6,7-dimethoxy-4-methyl-[1c], 7,8-dimethoxy-4-methyl-[1c], 4,7-dimethyl-[1d], 7-chloro-4-methyl-[1d], 4-phenyl-[1d], and 4-(4′-methylphenyl)[1d]-3-vinylquinolin-2(1*H*)-ones led respectively to **1b**, **1c**, **1d**, **1e**, **1f**, **1g**, and **1h**.

4-Methyl-3-vinylquinolin-2(1*H*)-thione (2a):
A mixture of **1a** (2.037 g, 10 mmol), thiourea (0.912 g, 12 mmol), and anhydrous ethanol (20 ml) were heated together under reflux for 3 h. The yellow crystalline solid that separated was collected, washed with little alcohol and heated with 10% aqueous sodium hydroxide (15 ml) at 80° for 15 min. On cooling and acidification, the quinolinethione was obtained as a yellow powder and was crystallised from chloroform. The thiones (**2b–h**) were likewise obtained from the respective chloroquinolines (**1b–h**) (For m.p., yield, etc. see Table 2).

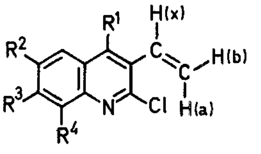
4-Methylthieno[2,3-*b*]quinoline (3a):
To a well-cooled and stirred solution of **2a** (1.005 g, 5 mmol) in anhydrous chloroform (30 ml) was added dropwise a chloroform solution (15 ml) containing bromine (0.8 g, 5 mmol). Thereafter it was stirred for 15 min. while the dibromide separated as a pale yellow powder. It was collected by filtration, washed with dry ether, and vacuum dried; yield: 1.55 g (86%); m.p., 255° (decomp.).
I.R. (KBr): $\nu_{max} = 1170\ cm^{-1}$.

The dibromide (500 mg) was suspended in anhydrous chloroform (50 ml), mixed with triethylamine (4 ml), and heated at reflux on a steam-bath for 1½ h. The solvent together with the excess triethylamine was stripped off. The residue was mixed with chloroform and washed with water. The organic layer was separated, dried (Na_2SO_4), and evaporated. Chromatography of the residue over alumina with benzene/petroleum ether (b.p. 60–80°) (1 : 1) furnished **3a** as colourless crystals; yield: 235 mg.

In another experiment, the reaction mixture containing the dibromide was mixed with triethylamine and refluxed for 1½ h. Work up of the product was done as above. The thienoquinolines (**3b–h**) were obtained from the respective quinolinethiones (**2b–h**) by a similar procedure as described for **3a**. (For yield, m.p., etc see Table 3).

4-Methyl-2,3-dihydrothieno[2,3-*b*]quinoline:
A mixture of 4-methyl-3-vinylquinoline-2(1*H*)-one (3.70 g, 20 mmol), tetraphosphorus decasulfide (5.5 g, 25 mmol), and pyri-

Table 1. 2-Chloro-3-vinylquinolines (**1**)



Compound	m.p.	Yield[a] (%)	Empirical Formula[b]	I.R. (KBr)[c] ν cm⁻¹	¹H-N.M.R. (CDCl$_3$)[d] δ ppm			
					H (a)	H (b)	H (x)	others
1a	68–69°	88	$C_{12}H_{10}ClN$ (203.7)	1620, 1550, 990, 920	5.37	5.73	6.89	2.65 (s, 3H, CH_3), 7.30–8.05 (m, 4H)
1b	101–102°	87	$C_{13}H_{12}NClO$ (233.8)	1610, 1560, 1000, 930	5.40	5.75	6.86	2.67 (s, 3H, CH_3), 7.87 (d, 1H, C-5-H, $J=9$ Hz), 7.20 (d.d, 1H, C-6-H, $J=2.5$ Hz, $J=9$ Hz), 3.95 (s, 3H, C-7-OCH_3), 7.34 (d, 1H, C-8-H, $J=2.5$ Hz)
1c	158–160°	88	$C_{14}H_{14}ClNO_2$ (263.7)	1620, 1560, 1000, 930	5.13	5.80	6.90	2.75 (s, 3H, CH_3), 7.30 (s, 1H, C-5-H), 4.03 (s, 6H, OCH_3), 7.23 (s, 1H, C-8-H)
1d	86–87°	81	$C_{14}H_{14}ClNO_2$ (263.7)	1610, 1560, 995, 920	5.43	5.78	6.93	2.68 (s, 3H, CH_3), 7.77 (d, 1H, C-5-H, $J=9$ Hz), 7.37 (d, 1H, C-6-H, $J=9$ Hz), 4.01, 4.17 (s, 6H, OCH_3)
1e	83–84°	88	$C_{13}H_{12}ClN$ (217.8)	1620, 1560, 1000, 930	5.43	5.62	6.90	2.65 (s, 3H, C-4-CH_3), 7.88 (d, 1H, C-5-H, $J=9$ Hz), 7.38 (d.d, 1H, C-6-H, $J=2.5$ Hz, $J=9$ Hz), 2.50 (s, 3H, C-7-CH_3), 7.82 (bs, 1H, C-8-H)
1f	86–87°	84	$C_{12}H_9Cl_2N$ (238.1)	1610, 1560, 995, 930	5.50	5.87	6.93	2.75 (s, 3H, CH_3), 7.97 (d, 1H, C-5-H, $J=9$ Hz), 7.54 (d.d, 1H, C-6-H, $J=2.5$ Hz, $J=9$ Hz), 8.03 (d, 1H, C-8-H, $J=2.5$ Hz),
1g	78–79°	89	$C_{17}H_{12}ClN$ (265.7)	1540, 990, 935	5.19	5.44	6.70	7.05–8.21 (m, 9H)
1h	122–123°	89	$C_{18}H_{14}ClN$ (279.8)	1540, 995, 940	5.22	5.47	6.70	2.45 (s, 3H, 4′-CH_3), 7.00–8.21 (m, 8H)

[a] Recrystallised from benzene/petroleum ether (b.p. 60–80°) (1:1).
[b] All products gave satisfactory elemental analyses (C ±0.13%, H ±0.12%, N ±0.12%).
[c] The last two peaks given are due to vinyl absorptions.
[d] The coupling constants J_{AX}, J_{BX}, J_{AB} were found to be 18, 11, and 2 Hz respectively for all compounds **1a**–**h**.

Table 2. 3-Vinylquinolin-2(1*H*)-thiones (**2**)

Compound	m.p.	Yield[a] (%)	Empirical Formula[b]	I.R. (KBr) ν cm⁻¹	
				>C=S	—CH=CH$_2$
2a	168–172°	89	$C_{12}H_{11}NS$ (201.3)	1180	990, 935
2b	160–165° (Sint. 144°)	85	$C_{13}H_{13}NOS$ (231.3)	1165	1000, 940
2c	171–174°	80	$C_{14}H_{15}NO_2S$ (261.3)	1170	1015, 940
2d	144–149°	86	$C_{14}H_{15}NO_2S$ (261.3)	1165	985, 920
2e	170–175° (Sint. 161°)	93	$C_{13}H_{13}NS$ (215.3)	1170	990, 925
2f	153–156°	85	$C_{12}H_{10}ClNS$ (235.7)	1175	995, 930
2g	189–190°	81	$C_{17}H_{13}NS$ (263.4)	1190	985, 930
2h	150–155°	86	$C_{18}H_{15}NS$ (277.4)	1190	995, 950

[a] Recrystallised from chloroform.
[b] All products gave satisfactory elemental analyses (C ±0.38%, H ±0.15%, N ±0.08%).

dine (50 ml) was refluxed for 6 h. It was cooled, poured into water, extracted with chloroform (3 × 150 ml), washed with water, and dried (Na_2SO_4). The solvent was evaporated and the residue was chromatographed over alumina with benzene/petroleum ether (b.p. 60–80°) (3:2) as eluent when 4-methyl-2,3-dihydrothieno[2,3-*b*]quinoline was obtained as colourless needles; yield: 400 mg (10%); m.p. 157–158° (benzene).

$C_{12}H_{11}NS$	calc.	C 71.60	H 5.51	N 6.96	S 15.92
(201.3)	found	71.22	5.39	6.84	15.63

Mass spectrum (70 eV): $m/e = 201$ ($M^{\oplus}$).

I.R. (KBr): $\nu_{max} = 1585\ cm^{-1}$.

¹H-N.M.R. (CDCl$_3$): $\delta = 2.60$ (s, 3H, CH_3), 3.50 (s, 4H, C-2, C-3-methylene protons[5]), 7.39–8.07 ppm (m, 4H).

Further elution of the column with chloroform afforded an yellow compound in 20% yield, identical in all respects with **2a**.

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Table 3. Thieno[2,3-*b*]quinolines (**3**)

Compound	m.p.	Yield[a] (%)	Empirical Formula[b]	^{1}H-N.M.R. ($CDCl_3$) δ ppm
3a	91–92°	85	$C_{12}H_9NS$ (199.3)	2.85 (s, 3H, CH_3), 7.28–8.33 (m, 6H)
3b	123–124°	94	$C_{13}H_{11}NOS$ (229.3)	2.70 (s, 3H, CH_3), 7.87 (d, 1H, C-5-H, $J=9$ Hz), 7.11 (d.d, 1H, C-6-H, $J=9$ Hz, $J=2.5$ Hz), 3.97 (s, 3H, C-7-OCH_3), 7.22–7.43 (m, 3H)
3c	191–192°	86	$C_{14}H_{13}NO_2S$ (259.3)	7.41 (d, 1H, C-2-H, $J=6$ Hz), 7.21 (d, 1H, C-3-H, $J=6$ Hz), 2.71 (s, 3H, CH_3), 7.36 (s, 1H, C-5-H), 4.00, 4.06 (s, 6H, OCH_3), 7.07 (s, 1H, C-8-H)
3d	149–150°	82	$C_{14}H_{13}NO_2S$ (259.3)	7.37 (d, 1H, C-2-H, $J=6$ Hz), 7.30 (d, 1H, C-3-H, $J=6$ Hz), 2.81 (s, 3H, CH_3), 7.80 (d, 1H, C-5-H, $J=9$ Hz), 7.29 (d, 1H, C-6-H, $J=9$ Hz), 4.04 (s, 3H, C-7-OCH_3), 4.18 (s, 3H, C-8-OCH_3)
3e	101–102°	87	$C_{13}H_{11}NS$ (213.3)	7.48 (d, 1H, C-2-H, $J=6$ Hz), 7.38 (d, 1H, C-3-H, $J=6$ Hz), 2.84 (s, 3H, C-4-CH_3), 8.00 (d, 1H, C-5-H, $J=9$ Hz), 7.37 (d.d, 1H, C-6-H, $J=9$ Hz, $J=2.5$ Hz), 2.58 (s, 3H, C-7-CH_3), 7.93 (bs, 1H, C-8-H)
3f	143–144°	90	$C_{12}H_8ClNS$ (233.7)	7.44 (d, 1H, C-2-H, $J=6$ Hz), 7.28 (d, 1H, C-3-H, $J=6$ Hz), 2.71 (s, 3H, CH_3), 7.79 (d, 1H, C-5-H, $J=9$ Hz), 7.25 (d.d, 1H, C-6-H, $J=9$ Hz, $J=2.5$ Hz), 7.96 (d, 1H, C-8-H, $J=2.5$ Hz)
3g	119–120°	80	$C_{17}H_{11}NS$ (261.2)	7.08 (d, 1H, C-3-H, $J=6$ Hz), 7.21–8.33 (m, 10H, C-2-H and other protons)
3h	166–167°	81	$C_{18}H_{13}NS$ (275.4)	7.11 (d, 1H, C-3-H, $J=6$ Hz), 2.48 (s, 3H, C-4′-CH_3), 7.21–8.33 (m, 9H, C-2-H and other pretons)

[a] Recrystallised from benzene/petroleum ether (b.p. 60–80°) (1:1).

[b] All products gave satisfactory elemental analyses (C ±0.15%, H ±0.15%, N ±0.09%, S ±0.12%).

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[5] The methylene proton absorptions of the dihydro derivative of **3** have similarly been reported[4] as an unresolved four-proton singlet.