The Synthesis of 2,3-Ring-Fused Analogues of 7-Fluoro-1-methyl-3-(methylsulfinyl)-4(1*H*)-quinolinone

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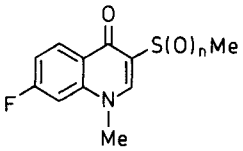
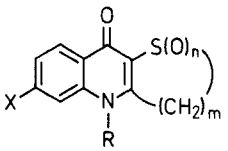
The lithium enolate of cyclic β-oxo sulfides has been shown to react with selected isatoic anhydrides to afford novel 9-oxothieno-, 10-oxothiopyrano- and 11-oxothiepino[3,2-*b*]quinolines. These cyclic sulfide compounds were then oxidized with 3-chloroperoxybenzoic acid to afford either the corresponding 1-oxides or 1,1-dioxides.

The quinolinone, 7-fluoro-1-methyl-3-(methylsulfinyl)-4(1*H*)-quinolinone (flosequinan, BTS 49465), is a clinically proven vasodilator which exerts both arterial and venous dilator effects.[1,2] It has also been shown that the sulfone metabolite (n = 2) of BTS 49465 has interesting pharmacological activity.[3] As part of our continuing interest in sulfur ring-fused derivatives of pharmacologically interesting molecules,[4-6] we report here our preparation of novel 2,3-ring-fused analogues of BTS 49465 (structure **A**).



n = 1, BTS 49465

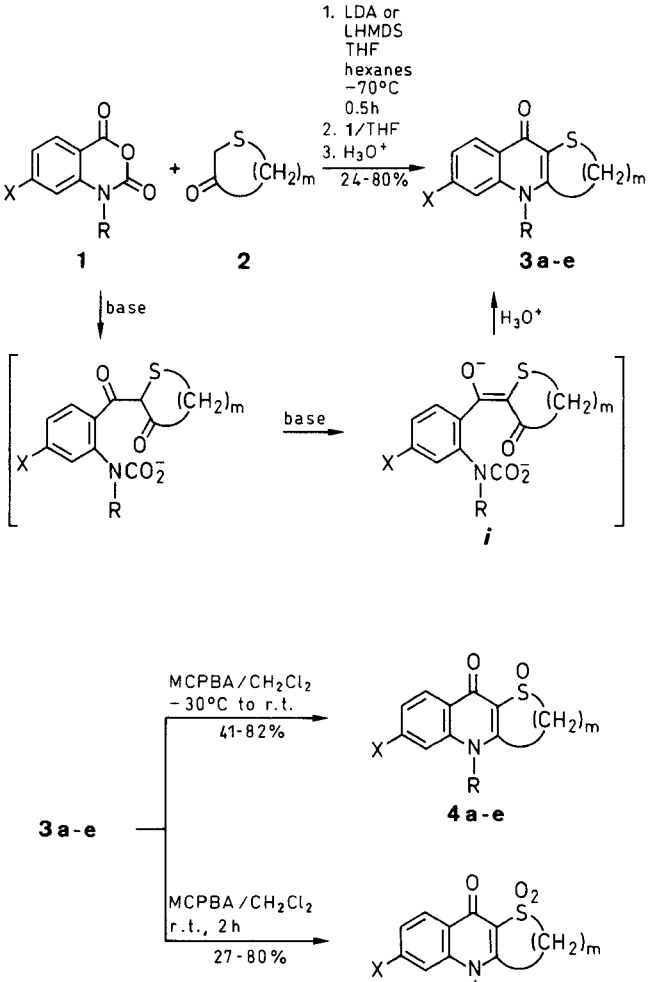


A

Our synthetic approach to **A** was based on previous reports of anion additions to isatoic anhydride.[7-10] The isatoic anhydride **1** (Scheme) was reacted with the lithium enolate of cyclic oxo sulfide **2** (2 equivalents) in tetrahydrofuran at −70 °C. This enolate reaction was found *not* to work with the corresponding oxo sulfone and that the base could be either lithium diisopropylamide (LDA) or lithium hexamethyldisilazide (LHMDS). The LDA reaction produced varying amounts of 2-aminomethyl-*N,N*-bis(1-methylethyl)benzamide (^{1}H NMR and mass spectrum analysis) while the LHMDS reaction produced very little of the corresponding amide side product. As reported earlier,[10] the second equivalent of enolate drives the reaction to the dianion form ***i*** which readily cyclizes to the quinolinone **3** when quenched with acid. The oxidation of sulfide **3** with one equivalent of 3-chloroperoxybenzoic acid (MCPBA) in dichloromethane at −30 °C afforded the sulfoxide **4** with very little over-oxidation to sulfone **5**. A non-aqueous workup gave the best results since **4** has unexpected water solubility. The sulfide **3** when treated with two equivalents of MCPBA in dichloromethane produced the sulfone **5** in fair to excellent yield. Here again a non-aqueous workup was best.

The spectral data for compounds prepared in this series are described in the Table.

The authors would like to thank Dr. M. L. Cotter and her staff for microanalytical and spectral data.



3–5	X	R	m	3–5	X	R	m
a	H	Me	2	**d**	H	Me	4
b	H	Me	3	**e**	F	Me	4
c	H	Bn	3				

Scheme

Melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 1430 instrument. ^{1}H NMR spectra were recorded at 300.1 MHz on a Bruker AC 300 spectrometer with TMS as internal standard. The elemental analyses were run on either a Perkin-Elmer 240C or 2400 instruments. All spectra are described in the Table and are in agreement with the structures cited. Standard flash column techniques (20 cm × 4.5 cm column) were employed to purify crude mixtures using 230–400 mesh. E. Merck silica gel under positive N_2 pressure. Tetrahydrothiophen-3-one, *N*-methylisatoic anhydride and *N*-benzylisatoic anhydride were obtained from commercial sources. Dihydrothiopyran-3-one,[11] thiepan-3-one[12] and 5-fluoro-*N*-methylisatoic anhydride[13] were prepared by literature methods.

2,3,4,9-Tetrahydro-4-methyl-9-oxothieno[3,2-*b*]quinoline (3a), 3,4,5,10-Tetrahydro-10-oxo-2*H*-thiopyrano[3,2-*b*]quinolines 3b,c and 2,3,4,5,6,11-Hexahydro-11-oxothiepino[3,2-*b*]quinolines 3d,e; General Procedure:

To a −5°C dry THF solution (5 mL) of freshly distilled $Me_3SiNHSiMe_3$ or *i*-Pr_2NH (4.4 mmol) under N_2 was slowly added BuLi in hexanes (4.4 mmol). After stirring for 30 min, the solution was cooled to −70°C and slowly treated with ketone **2** (4.4 equiv) dissolved in a minimal amount of THF (~5 mL). The resulting yellow solution was stirred at −70°C for 30 min and then quickly treated (addition temperature ≤ −40°C) with a THF solution (4 mL) of isatoic anhydride **1** (2.0 mmol). The mixture was allowed to warm to r.t. and was quenched with a saturated aqueous NH_4Cl solution (5 mL). This aqueous solution was extracted with CH_2Cl_2 (3 × 50 mL) and the combined organic phase was washed with brine and dried ($MgSO_4$). Solvent removal produced the crude product plus recovered ketone **2**. This crude material was purified by flash silica gel chromatography using 1–3% *i*-PrOH in CH_2Cl_2 to afford the desired product **3**. An analytical sample was obtained by recrystallization from the solvent shown in the Table.

Table. 2,3-Ring-Fused Compounds **3**, **4** and **5**

Compound	Yield[a] (%)	Reagent[b]	Molecular Formula[c]	mp (°C)[d] (solvent)	IR (KBr)[e] ν (cm^{-1})	^1H NMR[f] δ, J (Hz)
3a	24	LDA	$C_{12}H_{11}NOS$ (217.2)	224 shrinks 234–239 ($MeOH/CH_2Cl_2$)	2950, 1615, 1590, 1575, 1540, 770	(DMSO-d_6) 3.31 (t, 2H, J = 8.1, vinyl CH_2), 3.68 (t, 2H, J = 8.2, SCH_2), 3.81 (s, 3H, NCH_3), 7.36–7.41 (m, 1H, H-7), 7.70 (dt, 1H, J = 8.7, 1.5, H-6), 7.77 (d, 1H, J = 8.5, H-5), 8.15 (dd, 1H, J = 8.1, 1.4, H-8)
3b	72	LDA	$C_{13}H_{13}NOS$ (231.2)	217–223 (CH_2Cl_2/hexane)	2930, 1615, 1590, 1570, 1270, 770	($CDCl_3$) 2.20–2.28 (m, 2H, $CH_2CH_2CH_2$), 2.83–2.89 (m, 4H, SCH_2, vinyl CH_2), 3.71 (s, 3H, NCH_3), 7.30 (t, 1H, J = 7.4, H-8), 7.40 (d, 1H, J = 8.6, H-6), 7.55–7.61 (m, 1H, H-7), 8.40 (dd, 1H, J = 8.1, 1.6, H-9)
3c	47	LHMDS	$C_{19}H_{17}NOS$ (307.3)	195–204 (CH_2Cl_2/EtOAc)	2930, 1615, 1590, 1535, 1150, 760, 730, 700	($CDCl_3$) 2.12–2.18 (m, 2H, $CH_2CH_2CH_2$), 2.79 (t, 2H, J = 6.3, vinyl CH_2), 2.87 (t, 2H, J = 5.7, SCH_2), 5.42 (s, 2H, CH_2Ph), 7.03 (d, 2H, J = 6.7, H_{arom}), 7.21–7.48 (m, 6H, H_{arom}), 8.44 (dd, 1H, J = 8.1, 1.6, H-9)
3d	67	LHMDS	$C_{14}H_{15}NOS$ (245.3)	127.5–130 (CH_2Cl_2/Et_2O)	2930, 1615, 1590, 1570, 1520, 1185, 770	($CDCl_3$) 1.75–1.82 (m, 2H, methylene), 2.03–2.11 (m, 2H, methylene), 2.71–2.75 (m, 2H, vinyl CH_2), 3.43–3.47 (m, 2H, SCH_2), 3.84 (s, 3H, NCH_3), 7.36 (t, 1H, J = 7.5, H-9), 7.47 (d, 1H, J = 8.5, H-7), 7.61–7.66 (m, 1H, H-8), 8.48 (dd, 1H, J = 8.0, 1.4, H-10)
3e	80	LHMDS	$C_{14}H_{14}FNOS$ (263.3)	187.5–189.5 (CH_2Cl_2/Et_2O)	2910, 1625, 1585, 1520, 1450, 1270, 1195, 1070, 975, 770	($CDCl_3$) 1.79–1.84 (m, 2H, methylene), 2.03–2.11 (m, 2H, methylene), 2.71–2.75 (m, 2H, vinyl CH_2), 3.42–3.45 (m, 2H, SCH_2), 3.78 (s, 3H, NCH_3), 7.05–7.17 (m, 2H, H-7, H-9), 8.48 (dd, 1H, J = 8.8, 6.7, H-10)
4a	65	MCPBA	$C_{12}H_{11}NO_2S$ (233.2)	240–242 (dec) (EtOH)	2950, 1625, 1600, 1585, 1540, 1510, 1460, 1035, 780	(DMSO-d_6) 2.93–3.00 (m, 1H, methylene), 3.23–3.31 (m, 1H, methylene), 3.67–3.76 (m, 1H, methylene), 3.85 (s, 3H, NCH_3), 3.98–4.09 (m, 1H, methylene), 7.30–7.47 (m, 1H, H_{arom}), 7.80–7.89 (m, 2H, H_{arom}), 8.25 (d, 1H, J = 8.1, H-8)
4b	58	MCPBA	$C_{13}H_{13}NO_2S$ (247.2)	206–217 (dec) (EtOH)	2930, 1615, 1595, 1575, 1495, 1040, 1000, 780	(DMSO-d_6) 2.12–2.16 (m, 1H, methylene), 2.37–2.60 (m, 2H, methylene), 2.87–3.03 (m, 2H, methylene), 3.12–3.19 (m, 1H, methylene), 3.77 (s, 3H, NCH_3), 7.47 (d, 1H, J = 7.6, H-8), 7.80 (m, 1H, H-7), 7.88 (d, 1H, J = 8.6, H-6), 8.22 (dd, 1H, J = 8.0, 1.4, H-9)
4c	82	MCPBA	$C_{19}H_{17}NO_2S$ (323.3) (· 0.25 EtOH · 0.4 H_2O)[g]	166 (softens) 228–230 (dec)	2900, 1615, 1595, 1575, 1525, 1460, 1040, 990, 775, 725	(DMSO-d_6) 2.05–2.14 (m, 1H, methylene), 2.35–2.46 (m, 1H, methylene), 2.65 (t, 1H, J = 3.6, methylene), 2.90–3.05 (m, 3H, methylene), 5.67 (ABq, 2H, J_{AB} = 8.5, CH_2Ph), 7.10 (d, 2H, J = 7.4, H_{arom}), 7.26–7.47 (m, 4H, H_{arom}), 7.61–7.73 (m, 2H, H_{arom}), 8.26 (d, 1H, J = 7.7, H-9)
4d	41	MCPBA	$C_{14}H_{15}NO_2S$ (261.3)	203–205 (dec) (CH_2Cl_2/MeOH/Et_2O)	2920, 1615, 1595, 1575, 1515, 1455, 1405, 1185, 1030, 1005, 765	($CDCl_3$) 1.61–1.75 (m, 1H, methylene), 1.83–1.94 (m, 1H, methylene), 2.11–2.17 (m, 1H, methylene), 2.61–2.76 (m, 1H, methylene), 2.91–3.17 (m, 3H, methylene), 3.83 (s, 3H, NCH_3), 4.49 (ddd, 1H, J = 15.0, 11.9, 2.5, methylene), 7.41 (td, 1H, J = 7.2, 0.7, H-9), 7.54 (d, 1H, J = 8.6), 7.69 (ddd, 1H, J = 8.7, 7.0, 1.7, H-8), 8.40 (dd, J = 8.0, 1.6, 1H, H-10)
4e	48	MCPBA	$C_{14}H_{14}FNO_2S$ (279.3)	177–180.5 (CH_2Cl_2/Et_2O)	2920, 1625, 1595, 1560, 1525, 1445, 1270, 1195, 1035, 1010, 975, 770	($CDCl_3$) 1.62–1.94 (m, 2H, methylene), 2.11–2.18 (m, 1H, methylene), 2.64–2.76 (m, 1H, methylene), 2.89–3.19 (m, 3H, methylene), 3.78 (s, 3H, NCH_3), 4.51 (ddd, 1H, J = 15.0, 11.9, 2.4, methylene), 7.11–7.22 (m, 2H, H_{arom}), 8.43 (dd, J = 8.9, 6.6, 1H, H-10)
5a	39	MCPBA	$C_{12}H_{11}NO_3S$ (249.2)	293–294 (dec) (glacial AcOH)	2975, 1635, 1605, 1515, 1460, 1285, 1110, 780	(DMSO-d_6) 3.54 (s, 4H, methylene), 3.77 (s, 3H NCH_3), 7.51–7.56 (m, 1H, H-7), 7.83–7.92 (m, 2H H-5, H-6), 8.24 (dd, 1H, J = 8.1, 1.3, H-8)

Table. (continued)

Compound	Yield[a] (%)	Reagent[b]	Molecular Formula[c]	mp (°C)[d] (solvent)	IR (KBr)[e] ν (cm^{-1})	^1H NMR[f] δ, J (Hz)
5b	27	MCPBA	$C_{13}H_{13}NO_3S$ (263.2)	> 300 (H_2O wash)	2990, 1620, 1600, 1525, 1310, 1285, 1260, 1110, 765	(DMSO-d_6) 2.00–2.33 (m, 2H, $CH_2CH_2CH_2$), 3.14 (t, 2H, J = 6.1, vinyl CH_2), 3.24–3.32 (m, 2H, SO_2CH_2), 3.76 (s, 3H, NCH_3), 7.47 (t, 1H, J = 6.9, H-8), 7.81 (td, 1H, J = 6.7, 1.5, H-7), 7.87 (d, 1H, J = 8.6, H-6), 8.18 (dd, 1H, J = 6.6, 1.5, H-9)
5c	63	MCPBA	$C_{19}H_{17}NO_3S$ (339.3)	300–301.5 (dec) (glacial AcOH)	1615, 1595, 1520, 1480, 1290, 1260, 1115, 875, 770	(DMSO-d_6) 2.24–2.28 (m, 2H, $CH_2CH_2CH_2$), 3.06 (br s, 2H, vinyl CH_2), 3.29–3.33 (m, 2H, SO_2CH_2), 5.64 (s, 2H, CH_2Ph), 7.14 (d, 2H, J = 7.1, H_{arom}), 7.27–7.47 (m, 4H, H_{arom}), 7.60 (d, 1H, J = 8.5, H-6), 7.67–7.72 (m, 1H, H-7), 8.22 (dd, 1H, J = 8.0, 1.6, H-9)
5d	69	MCPBA	$C_{14}H_{15}NO_3S$ (277.3)	266–269 (glacial AcOH)	2940, 1615, 1600, 1510, 1280, 1265, 1260, 1105, 810, 770	(DMSO-d_6) 1.89–2.27 (m, 4H, methylene), 3.34–3.39 (m, 4H, vinyl CH_2, SO_2CH_2), 3.84 (s, 3H, NCH_3), 7.47 (t, 1H, J = 7.1, H-9), 7.76–7.82 (m, 1H, H-8), 7.88 (d, 1H, J = 8.6, H-7), 8.16 (dd, 1H, J = 8.0, 1.4, H-10)
5e	80	MCPBA	$C_{14}H_{14}FNO_3S$ (295.3)	298–300 (EtOH(trit)]	2050, 1635, 1615, 1460, 1285, 1200, 1125, 1110, 840, 775, 710	(DMSO-d_6) 1.88–2.27 (m, 4H, methylene), 3.31–3.42 (m, 4H, vinyl CH_2, SO_2CH_2), 3.80 (s, 3H, NCH_3), 7.33 (td, 1H, J = 8.6, 2.2, H-9), 7.78 (dd, 1H, J = 11.9, 2.1, H-7), 8.20 (dd, 1H, J = 8.8, 6.8, H-10)

[a] The yield is not optimized and is that of isolated product.
[b] LDA = lithium diisopropylamide, LHMDS = lithium hexamethyldisilazide, MCPBA = 3-chloroperoxybenzoic acid.
[c] Satisfactory microanalysis obtained: C ± 0.24 (exc. **4e** −0.36 and **5d** −0.40), H ± 0.29, N ± 0.30.
[d] Uncorrected.
[e] Recorded on a Perkin-Elmer 1430 spectrophotometer.
[f] Recorded at 300.1 MHz on a Bruker AC 300 spectrometer.
[g] For compound **4c** the mass spectrum was obtained on a Finnigan Mat 8230 and shows m/z = 324 (MH^+, 100).

Thieno-, Thiopyrano- and Thiepino[3,2-*b*]quinoline 1-Oxides 4a–e; General Procedure:

To a −30 °C solution of sulfide **3** (1.0 mmol) in CH_2Cl_2 (7 mL) under N_2 was added MCPBA (85%, 1.0 mmol) in one portion. After the resulting yellow solution had warmed to r.t., the solvent was removed in vacuo and the residue was slurried in a minimal amount of hot EtOH (~ 5 mL). The solid was isolated and an analytical sample was obtained by recrystallization from the solvent shown in the Table.

Thieno-, Thiopyrano- and Thiepino[3,2-*b*]quinoline 1,1-Dioxides 5a–e; General Procedure:

To a −30 °C solution of sulfide **3** (1.0 mmol) in CH_2Cl_2 (7 mL) under N_2 was added MCPBA (85%, 2.2 mmol) in one portion. After stirring at r.t. for 2 h, the solvent was removed in vacuo and the residue was slurried in a minimal amount of hot EtOH (~ 5 mL). A tan solid was collected and recrystallized from the solvent listed in the Table to obtain the analytical sample.

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