Synthesis, Phosphodiesterase Inhibition and Antiinflammatory Activity of 2-Aryl-3-hydroxythieno[2,3-*b*]quinoline 1,1-Dioxides. Application of Sodium Chlorite as a Novel Reagent for the (Stepwise) Oxidation of Sulfides to Sulfones.

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Synthesis of five 2-aryl-3-hydroxythieno[2,3-*b*]quinoline 1,1-dioxides (**38-42**) from 3-formylquinoline-2-thiol (**3**) *via* a facile oxidation-cyclization sequence is reported. Reaction of appropriate benzyl chlorides with the thiol (**3**) in the presence of sodium methoxide gave excellent yields of the corresponding benzyl 2-(3-formylquinolyl) sulfides (**4-8**). Direct oxidation of these sulfides to the corresponding sulfones (**23-27**) was effected with excess sodium chlorite in aqueous pyridine. Esterification of these sulfone-acids followed by brief treatment of the resulting esters **28-32** with sodium methoxide gave the desired compounds **38-42** after acidification. The benzyl 2-(3-formylquinolyl) sulfides were also selectively oxidized to the corresponding sulfoxides (**13-17**). Thus sodium chlorite has proved to be an effective reagent for the stepwise oxidation of sulfides to sulfones. The title compounds were potent inhibitors of cyclic AMP phosphodiesterase, but failed to display significant antiinflammatory effects in the carrageenan rat paw edema test or significant activity in the phenylquinone induced writhing test for analgesia.

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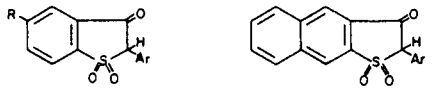
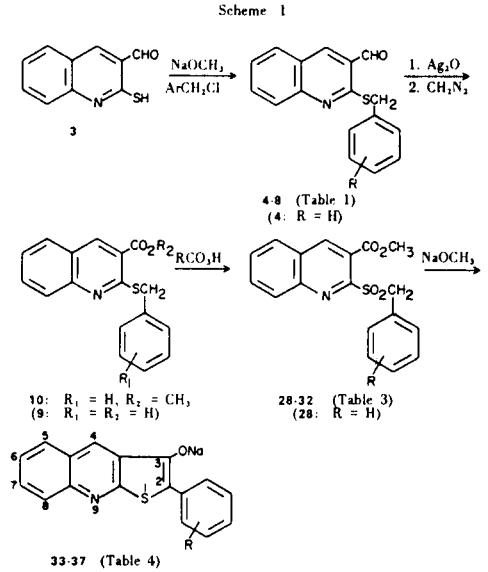
We have recently become interested in the synthesis of novel heterocyclic systems for evaluation of their therapeutic potential, particularly as nonsteroidal antiinflammatory agents. In conjunction with this program, we wish to report results of our initial synthetic and biological studies concerning compounds of the thieno[2,3-*b*]-quinoline series. Aside from a multistep entry into this series from a butryolactone derivative reported some time ago (2), and several simple representatives prepared more recently (3-5), the chemistry of this ring system has remained uninvestigated. Our interest in this ring system stems from the reported (6) antiinflammatory activity shown by a number of 2-arylbenzo[*b*]thiophene-3(2*H*)-one 1,1-dioxides (**1**) and two 2-arylnaphtho[2,3-*b*]-thiophene-3(2*H*)one 1,1-dioxides (**2**). We now report synthesis, *via* a facile oxidation-cyclization procedure, of



1 2

a group of 2-aryl-3-hydroxythieno[2,3-*b*]quinoline 1,1-dioxides (**38-42**) which can be viewed as aza congeners of the antiinflammatory naphtho[2,3-*b*]thiophene derivatives (**2**). We also report biological evaluation of these compounds for *in vivo* antiinflammatory activity in the carrageenan rat paw edema test, analgesic activity in the phenylquinone induced writhing test, and *in vitro* inhibition of bovine heart cyclic AMP phosphodiesterase.

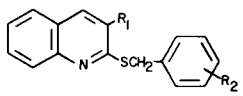
Scheme I



Our synthetic approach to the desired compounds (**38-42**, Table 4) proceeded through intermediates similar to those employed in one route (6) to the antiinflammatory compounds **1** and **2**. We envisioned (Scheme I) treatment of the readily available sodium salt of **3** with the corresponding benzyl chlorides to provide **4-8**, since **4** had previously been prepared by this method (3). It seemed likely to us that the oxidation states of **4-8** could be adjusted to give, after esterification of an appropriate intermediate, the sulfone-esters **28-32**. Although two

Table 1

Benzyl 2-(3-Formylquinolyl) Sulfides and Other Related Sulfides

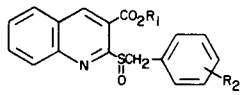


Compound	R_1	R_2	Yield % (a)	M.p. °C (Recrystallization Solvent)	Formula	Analyses or Literature Melting Point C Calcd.	C Found	H Calcd.	H Found	N Calcd.	N Found
4	CHO	H	88	108-110 (Acetonitrile)	$C_{17}H_{13}NOS$	104° (b)					
5	CHO	4-Cl	91	143-145 (Benzene)	$C_{17}H_{12}ClNOS$	65.06	64.77	3.85	3.79	4.46	4.51
6	CHO	3-F	92	127-129 (Benzene)	$C_{17}H_{12}FNOS$	68.66	68.90	4.07	4.07	4.71	4.74
7	CHO	4-F	90	128-129 (Benzene)	$C_{17}H_{12}FNOS$	68.66	68.48	4.07	3.96	4.71	4.98
8	CHO	4-OCH_3	92	108-110 (Acetonitrile)	$C_{18}H_{15}NO_2S$	69.88	69.93	4.89	4.84	4.52	4.52
9	CO_2H	H	98	266-268 dec. (DMSO-Acetic Acid) (c)	$C_{17}H_{13}NO_2S$	69.13	69.20	4.44	4.65	4.74	4.54
10	CO_2Me	H	92	129-131 (Acetonitrile)	$C_{18}H_{15}NO_2S$	69.88	69.92	4.89	4.74	4.53	4.58
11	CO_2H	4-OCH_3	99	233-235 dec. (DMSO-Acetic Acid) (c)	$C_{18}H_{15}NO_3S$	66.44	66.75	4.65	4.80	4.31	4.13
12	CO_2Me	4-OCH_3	88	146-148 (Acetonitrile)	$C_{19}H_{17}NO_3S$	67.23	67.07	5.05	4.93	4.13	4.31

(a) Crude but essentially pure material. (b) Reference 3. (c) Recrystallized by dissolving the dry acid in a small volume of DMSO and diluting with several volumes of acetic acid.

Table 2

Benzyl 2-(3-Carboxyquinolyl) Sulfoxides and Methyl Esters

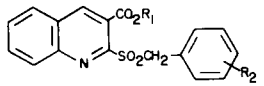


Compound	R_1	R_2	Yield % (a)	M.p. °C (Recrystallization Solvent)	Formula	Analyses C Calcd.	C Found	H Calcd.	H Found	N Calcd.	N Found
13	H	H	96	200-203 dec. (DMSO-Acetic Acid) (b)	$C_{17}H_{13}NO_3S$	65.58	65.86	4.21	4.20	4.50	4.46
14	H	4-Cl	85	187-190 dec. (DMSO-Acetic Acid) (b)	$C_{17}H_{12}ClNO_3S$	59.04	59.30	3.50	3.66	4.05	4.04
15	H	3-F	88	207-209 dec. (DMSO-Acetic Acid) (b)	$C_{17}H_{12}FNO_3S$	61.99	61.61	3.67	3.80	4.25	4.09
16	H	4-F	84	195-197 dec. (DMSO-Acetic Acid) (b)	$C_{17}H_{12}FNO_3S$	61.99	61.88	3.67	3.76	4.25	4.25
17	H	4-OCH_3	98	143-145 dec. (DMSO-Acetic Acid) (b)	$C_{18}H_{15}NO_4S$	63.32	63.49	4.43	4.40	4.10	4.23
18	CH_3	H	97	150.5-151.5 (Benzene-Hexane)	$C_{18}H_{15}NO_3S$	66.44	66.38	4.65	4.46	4.30	4.44
19	CH_2	4-Cl	69	143-145 (Benzene-Hexane)	$C_{18}H_{14}ClNO_3S$	60.08	60.07	3.92	3.98	3.89	3.96
20	CH_3	3-F	91	145-146 (Benzene-Hexane)	$C_{18}H_{14}FNO_3S$	62.96	62.97	4.11	4.31	4.08	3.97
21	CH_3	4-F	88	158.5-159.5 (Benzene-Hexane)	$C_{18}H_{14}FNO_3S$	62.96	62.64	4.11	4.18	4.08	4.19
22	CH_3	4-OCH_3	93	133-135 (Ethyl Acetate)	$C_{19}H_{17}NO_4S$	64.39	64.20	4.84	4.92	3.95	3.70

(a) Crude but essentially pure material. (b) Recrystallized by dissolving the dry acid in a small volume of DMSO and diluting with the specified cosolvent. The decomposition point of this acid was somewhat dependent on the rate of heating which in this determination was approximately 10°/minute.

Table 3

Benzyl 2-(3-Carboxyquinolyl) Sulfones and Methyl Esters

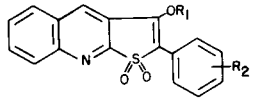


Compound	R_1	R_2	Yield %	M.p. °C (Recrystallization Solvent)	Formula	Analyses C Calcd.	C Found	H Calcd.	H Found	N Calcd.	N Found
23	H	H	65 (a)	198-202 dec. (DMSO-Acetic Acid) (b)	$C_{17}H_{13}NO_4S$	62.37	62.02	4.00	4.20	4.28	4.38
24	H	4-Cl	69 (a)	209-211 dec. (DMSO-Methanol) (b)	$C_{17}H_{12}ClNO_4S$	56.43	56.68	3.34	3.20	3.87	3.67
25	H	3-F	80 (a)	205-209 dec. (DMSO-Acetic Acid) (b)	$C_{17}H_{12}FNO_4S$	59.12	59.02	3.50	3.62	4.06	3.99
26	H	4-F	65 (a)	204-207 dec. (DMSO-Acetic Acid) (b)	$C_{17}H_{12}FNO_4S$	59.12	58.99	3.50	3.64	4.06	4.13
27	H	4-OCH_3	12 (a)	184-186 dec. (DMSO-Acetic Acid) (b)	$C_{18}H_{15}NO_5S$	60.49	60.66	4.23	4.14	3.92	3.63
28	CH_3	H	84 (c)	152-5-153.5 (Benzene-Hexane)	$C_{18}H_{15}NO_4S$	63.33	63.06	4.43	4.56	4.10	4.08
29	CH_3	4-Cl	83 (c)	126-128 (Benzene-Hexane)	$C_{16}H_{14}ClNO_4S$	57.52	57.84	3.75	3.89	3.73	4.11
30	CH_3	3-F	78 (c)	157.5-158.5 (Benzene-Hexane)	$C_{18}H_{14}FNO_4S$	60.16	60.25	3.93	3.91	3.90	3.86
31	CH_3	4-F	87 (c)	156.5-157.5 (2-Propanol)	$C_{18}H_{14}FNO_4S$	60.16	60.11	3.93	4.09	3.90	3.99
32	CH_3	4-OCH_3	44 (c,d)	110-112 (Ethanol)	$C_{19}H_{17}NO_5S$	61.44	61.49	4.61	4.56	3.77	3.74

(a) Crude but essentially pure material. (b) Recrystallized by dissolving the dry acid in a small volume of DMSO and adding several volumes of the specified cosolvent. The decomposition point of this acid was somewhat dependent on the rate of heating which in this case was approximately 10°/minute. (c) Recrystallized. (d) By oxidation of the ester **12** with *m*-chloroperbenzoic acid.

Table 4

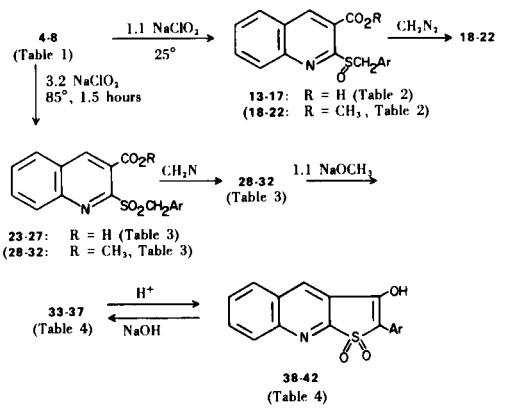
2-Aryl-3-hydroxythieno[2,3-*b*]quinoline 1,1-Dioxides and Sodium Salts



Compound	R_1	R_2	Yield %	M.p. °C (Recrystallization Solvent)	Formula	Analyses C Calcd.	C Found	H Calcd.	H Found	N Calcd.	N Found
33	Na	H	84 (b)	> 320 (Methanol)	$C_{17}H_{10}NO_3SNa$	61.62	61.54	3.04	3.12	4.23	4.29
34	Na	4-Cl	94 (b)	> 320 (Ethanol)	$C_{17}H_9ClNO_3SNa$	55.82	55.55	2.48	2.58	3.83	3.72
35	Na	3-F	94 (b)	> 320 (Methanol)	$C_{17}H_9FNO_3SNa$	58.45	58.48	2.60	2.48	4.01	4.11
36	Na	4-F	86 (b)	> 320 (Methanol)	$C_{17}H_9FNO_3SNa$	58.45	58.57	2.60	2.48	4.01	4.07
37	Na	4-OCH_3	(c)	> 320 (Methanol))	$C_{18}H_{12}NO_4SNa$	59.83	59.93	3.35	3.53	3.88	3.90
38	H	H	(d)	240.5-242.5 (Acetic Acid)	$C_{17}H_{11}NO_3S$	66.00	66.12	3.59	3.82	4.53	4.68
39	H	4-Cl	(d)	242-5-244.5 (Acetic Acid)	$C_{17}H_{10}ClNO_3S$	59.40	59.59	2.93	3.07	4.08	4.20
40	H	3-F	(d)	241-243 (Acetic Acid)	$C_{17}H_{10}FNO_3S$	62.38	62.23	3.08	3.03	4.28	4.12
41	H	4-F	(d)	228-230 (Acetic Acid)	$C_{17}H_{10}FNO_3S$	62.38	62.33	3.08	3.19	4.23	4.37
42	H	4-OCH_3	74 (e)	226.5-228.5 (Acetic Acid)	$C_{18}H_{13}NO_4S$	63.70	63.40	3.86	3.97	4.13	4.36

(a) Crude but essentially pure material. (b) After drying to constant weight in high vacuum at 150°. (c) Isolated as **42**. (d) Essentially quantitative by acidification (excess 37% hydrochloric acid) of a 1:1 methanol-water solution of the corresponding sodium salt and dilution with water. (e) By acidification of the reaction mixture with 37% hydrochloric acid.

Scheme 2



potentially serious competing reactions were anticipated (see below), treatment of **28-32** with sodium methoxide was expected to yield the sodium salts **33-37**, since precedent for a similar cyclization exists in non-heterocyclic systems (6-8).

Accordingly, *S*-benzylation of **3** with various benzyl chlorides, employing a modification of the method of Hull (3), gave the sulfides **4-8** in high yield. Initial exploratory work (Scheme I) with **4** indicated that the aldehyde function could be oxidized to the acid **9** with silver oxide in aqueous tetrahydrofuran. The sulfone ester **28** was then found to result from esterification of **9** with diazomethane, followed by oxidation of the resulting sulfide-ester **10** with a slight excess of *m*-chloroperbenzoic acid in chloroform. Although the results of this exploratory work appeared promising, we initially desired a convenient procedure for the direct oxidation of **4-8** to sulfone-acids **23-27** (Scheme 2). A possible reagent for this transformation appeared to be potassium permanganate. However, we were interested in avoiding the potential experimental difficulties (9) associated with large scale oxidations of this type. In the course of investigating other possible reagents, we found that when the sulfides **4-8** were treated with slightly more than the calculated amount (1.1 molar equivalents) of sodium chlorite in 90% pyridine containing a catalytic amount of 37% hydrochloric acid, the sulfide function was exothermically oxidized in 20 minutes to the corresponding sulfoxide with concomitant oxidation of the aldehyde function to the carboxylic acid. The resulting sulfoxide-acids **13-17** were obtained in high yield with essentially no overoxidation to the sulfones and were readily esterified with diazomethane to the corresponding esters **18-22**.

In each case the nmr spectrum of the sulfoxides **13-22** showed a well-defined AB system for the methylene protons. Magnetic nonequivalence of methylene protons adjacent to a sulfoxide function is well known (10-13). However, a number of examples of apparent equivalence of such protons have been reported in systems similar to **13-22** (14-16). For example, Nishio (15,16) reported that for certain members of a series of benzyl phenyl sulfoxides in deuteriochloroform (and other solvents), no geminal coupling of the methylene protons was observed and thus these protons appeared to be equivalent. The magnetic nonequivalence of methylene protons in this series was found to have a strong, complicated dependence on the dielectric constant of the solvent and the electronic nature of the aromatic substituents. Although we have not made a detailed study of solvent effects, no apparent equivalence or near equivalence of the methylene protons of **13-17** (in dimethyl sulfoxide-d_6) or of **18-22** (in deuteriochloroform) was observed. In the sulfoxides **13-22**, separation of the methylene protons was in the range 0.40-0.64 δ and the observed coupling constants for these protons (J = 12.0-13.0 Hz) were of the magnitude expected.

Except in the case of the 4-methoxybenzyl derivative, **27**, the sulfone acids **23-27** were also obtained in good yield when the sulfides **4-8** were oxidized with excess (3.2 molar equivalents) of sodium chlorite at 80-90° for 1.5 hours. Esterification of these acids with diazomethane then provided the direct precursors, **28-32**, of the sodium salts **33-37** of **38-42**.

A search of the literature revealed that sodium chlorite has been utilized for the oxidation of phenolic aldehydes to the corresponding acids (17) and in the oxidation of carbohydrates (18) but otherwise has received little attention (19) in preparative organic chemistry. To our knowledge, no examples of the oxidation of sulfides to sulfoxides and sulfones using this reagent have been reported. In view of the successful applications described above (except efficient conversion of **8** to **27**, see below) this material provides a new reagent for this stepwise oxidative sequence and may be especially valuable when concomitant oxidation of the aldehyde and sulfide function is desired. The scope of this reaction is under investigation and will be reported in due course.

Although the sulfone acid **27** could be obtained directly from the sulfide **8** by this method, the required ester **32**, of **27** was best prepared using the two-stage oxidative sequence initially employed for conversion of **4** to **28** (Scheme I).

Cyclization of sulfone esters similar to **28-32** has been easily accomplished previously with sodium methoxide in methanol (6-8); however, this precedent was established for non-heterocyclic precursors to the cyclic β-keto-sulfones. We considered displacement of the sulfonyl group in **28-32**, or in the cyclized materials **33-37**, by methoxide ion as possible competing reactions in view of the kinetic results of Barlen (20) who found that methoxide ion readily displaced the methanesulfonyl group located in the 2- and 4-positions of the quinoline nucleus.

Table 5 (a)

Inhibition of Bovine Heart Phosphodiesterase

Compound (b)	I_{50} X 10^4 M (c,d)
33	3.6 (2.4-4.7)
34	2.2 (1.6-2.8)
35	2.3 (1.5-3.2)
36	3.5 (1.7-5.3)
37	4.6 (2.9-6.3)
Indomethacin	1.9 (1.3-2.5)
Theophylline	6.2 (5.0-7.3)

(a) For procedure see experimental. (b) Compounds **23-25** at 500 μm showed less than 10% inhibition. (c) Numbers in parentheses represent the 95% confidence intervals. (d) Substrate concentration was 100 μm.

In order to avoid possible complications of this type, we employed only a slight excess of sodium methoxide and short (0.5 hour) reaction time for the cyclization of **28-32** and were able to obtain the sodium salts **33-37** in high yield. The conjugate acids **38-42**, obtained by acidification of aqueous methanolic solutions of the sodium salts appear to exist in the enol form (hydroxyl and no carbonyl absorption in the infrared). These compounds easily dissolved in aqueous sodium hydroxide to regenerate the corresponding sodium salts **33-37** but were difficultly soluble in the usual organic solvents and consequently not readily recrystallized. In contrast, the sodium salts **33-37** were bright orange solids which except **34**, were readily recrystallized from methanol and were obtained as methanol solvates. The compounds tenaciously retained methanol of crystallization which could be completely removed only by drying in high vacuum at 150-160°

Biological.

Because of their similarity to a series of antiinflammatory **1** and **2** (6), we expected that **33-42** might possess significant antiinflammatory activity. Furthermore, because of the large sample requirements for *in vivo* evaluation we sought a simple *in vitro* test to guide our synthetic efforts in target compound selection. Stefanovich (21) has reported that the potency of acidic antiinflammatory agents correlates well with their ability to inhibit bovine heart cyclic AMP phosphodiesterase. The anti-phosphodiesterase effects of nonsteriodal antiinflammatory agents has been recently reviewed (22).

Compounds **33-37** (Table 5, the salts were used due to greater solubility) were indomethacin-like in their ability to inhibit the enzyme and significantly more potent than the standard phosphodiesterase inhibitor, theophylline. Open ring analogs **23-26** were inactive. Changes in the substitution pattern on the phenyl substituent had relatively little effect on I_{50}.

Using the carrageenan rat paw edema test essentially as described by Winter (23), **38-42** failed to show significant acute antiinflammatory activity. Thus, in this series our results indicate no correlation between inhibition of phosphodiesterase and *in vivo* antiinflammatory activity. These compounds were also essentially inactive in the mouse phenylquinone-induced writhing test (24) for analgesia, but do constitute a potent new class of cyclic AMP phosphodiesterase inhibitors.

EXPERIMENTAL

Melting points (corrected) were determined in open capillary tubes. Microanalyses were performed by the Laboratory's Section on Microanalytical Services and Instrumentation. Ir (Perkin-Elmer 21), mass (Hitichi Perkin-Elmer RMU-6E; 70 ev) and nmr (Varian A-60; TMS internal reference) spectra were consistent with the assigned structures. Sodium chlorite (80%) was purchased from Alpha Products division of Ventron Corporation, Danvers, MA 01923. Optimization of yields was not attempted in this work. Bovine heart phosphodiesterase was purchased from Sigma Chemical Co.; [8-^{3}H]cyclic AMP, specific activity 30 Ci/mmole, was obtained from Amersham Searle Corp.; [^{14}C] 5'-AMP, specific activitv 570 mCi/mmole, was obtained from New England Nuclear Co.

Enzyme Studies.

The assay procedure of Klee (25) was used in this work. The cyclic AMP phosphodiesterase was shown *via* a Lineweaver-Burke plot to contain both high and low Km activities comparable to those reported (26,27). Initial rate measurements were linear with enzyme concentration and time (to 40 minutes). Inhibitor studies were conducted at a cyclic AMP concentration of 100 μm. I_{50}'s were determined by plotting uninhibited velocity/inhibited velocity ($Vo/_V$) versus inhibitor concentration (28). The I_{50} is the inhibitor concentration giving $Vo/_V$ = 2. Normally, five inhibitor concentrations giving 25-75% inhibition of the enzyme were used. Each assay was repeated with fresh inhibitor solutions and data was pooled. The 95% confidence intervals for the I_{50}'s were determined from the 95% confidence intervals for the line generated by the $Vo/_V$ versus inhibitor concentration plots. An equivalent of sodium hydroxide solution was used to solubilize indomethacin. The buffer capacity of the assay buffer (0.05 N Tris, *p*H 8.0) was sufficient to resist potential *p*H changes that could be caused by the inhibitors.

Benzyl 2-(3-Formylquinolyl) Sulfides (**4-8**). (Table 1).

These compounds were prepared from 3-formylquinoline-2-thiol (**3**) (3). The general procedure for 3-fluorobenzyl 2-(3-formylquinolyl) sulfide (**6**) was developed from, and gave better results than, that employed by Hull (3) for synthesis of **4**.

To a stirred suspension of the thiol **3** (9.45 g., 50.0 mmoles) in dry dimethylformamide (150 ml.) was added sodium methoxide (2.85 g., 52.7 mmoles). The reaction mixture was warmed to 40° and stirred several minutes until the solids had dissolved. To the resulting blood-red solution was added 3-fluorobenzyl chloride (8.64 g., 60 mmoles). A moderately exothermic reaction ensued, and the initial red color was rapidly discharged to give a light orange solution. After stirring 0.5 hours, 10% sodium hydroxide (100 ml.) was added, followed by sufficient ice to give a final volume of 500 ml. The resulting solid material was filtered, washed well with water, then hexane and dried to give crude, nearly pure **6** (13.6 g., 92%), m.p. 123-135.5°. Recrystallization

gave pure **6**; mass spectrum: m/e 297 (M^+); ir (nujol): 1685 cm^{-1} (C=O); nmr (deuteriochloroform): δ 4.62 (s, 2H, CH_2), 6.66-8.16 (m, 8H, ArH), 8.40 (s, 1H, quinoline-4H), and 10.26 (s, 1H, CHO).

Benzyl 2-(3-Carboxyquinolyl) Sulfoxides (**13-17**) and the Corresponding Methyl Esters **18-22**.

The following procedure for 3-fluorobenzyl 2-(3-carboxyquinolyl) sulfoxide (**15**) and the corresponding methyl ester **20** is representative.

The crude sulfide **6** (892 mg., 3.0 mmoles) was dissolved in a solution of pyridine (15 ml.) and water (3 ml.). After addition of 37% hydrochloric acid (2 drops), a solution of 80% sodium chlorite (373 mg., 3.3 mmoles) in water (3 ml.) was added dropwise with cooling to maintain the temperature of the reaction mixture in the range 22-28°. After stirring 0.5 hour, the mixture was diluted with water (100 ml.) and extracted with ether (100 ml.). The aqueous phase was removed, acidified with 37% hydrochloric acid, and the resulting white solid was filtered, washed well with water and dried to give essentially pure **15** (869 mg., 88%). The analytical sample was prepared by dissolving the dry material in warm dimethyl sulfoxide and diluting with three volumes of methanol; mass spectrum: m/e 329 (M^+); ir (nujol); 1695 cm^{-1} (C=O); nmr (DMSO-d_6): δ 3.99 and 4.58 (1H each, AB quartet centered at 4.28, J = 13.0 Hz, CH_2S=O), 7.00-7.58 (m, 4H, ArH), 7.73-8.50 (m, 4H, ArH) and 9.13 (s, 1H, quinoline-4H). Treatment of **15** (576 mg., 1.75 mmoles) with excess diazomethane in ether-chloroform gave the methyl ester **20** (545 mg., 91%) after recrystallization from benzene-hexane; mass spectrum: m/e 343 (M^+); ir (nujol): 1710 cm^{-1} (C=O); nmr (deuteriochloroform): δ 4.05 (s, 3H, OCH_3), 4.08 and 4.60 (1H each, AB quartet centered at 4.33, J = 12.5 Hz, CH_2S=O), 6.90-7.40 (m, 4H, ArH), 7.66-8.63 (m, 4H, ArH) and 9.05 (s, 1H, quinoline-4H).

Benzyl 2-(3-Carboxyquinolyl) Sulfones (**23-27**) and the Corresponding Methyl Esters **28-32**.

These compounds were prepared using the general procedure described below for 3-fluorobenzyl 2-(3-carboxyquinolyl) sulfone (**25**) and the corresponding methyl ester **30**.

The sulfide **6** (10.40 g., 35.0 mmoles) was dissolved in a mixture of pyridine (100 ml.), water (20 ml.) and 37% hydrochloric acid (0.5 ml.). A solution of 80% sodium chlorite (13.05 g., 115.5 mmoles) in water (50 ml.) was added dropwise (stirring) with cooling to maintain a temperature of <50°. When the addition was complete the stirred solution was heated at 75-85° for 1.5 hours, cooled, diluted with water (200 ml.) and extracted with ether (200 ml.) which was discarded. The aqueous phase was acidified with 37% hydrochloric acid and the resulting solid was filtered, washed well with water and dried to give nearly pure **25** (9.68 g., 80%). For recrystallization, **25** was dissolved in warm dimethylsulfoxide and the solution was diluted with three volumes of acetic acid to give pure **25**; mass spectrum: m/e 345 (M^+); ir (nujol): 1715 cm^{-1} (CO_2H); nmr (DMSO-d_6): δ 5.23 (s, 2H, CH_2), 7.00-8.63 (m, 8H, ArH) and 9.00 (s, 1H, quinoline-4H). Treatment of the sulfone-acid **25** (690 mg., 2.0 mmoles) with excess diazomethane in ether-chloroform gave the corresponding ester **30** (563 mg., 78%) after recrystallization from benzene-hexane; mass spectrum: m/e 359 (M^+); ir (nujol): 1712 cm^{-1} (C=O); nmr (deuteriochloroform): δ 4.02 (s, 3H, OCH_3), 4.98 (s, 2H, CH_2), 6.88-7.40 (m, 4H, ArH), 7.68-8.46 (m, 4H, ArH) and 8.63 (s, 1H, quinoline-4H).

Sodium Salts of 2-Aryl-3-hydroxythieno[2,3-*b*]quinoline 1,1-Dioxides (**33-37**) and Conjugate Acids **38-42**.

The sulfone esters **28-32** were cyclized to the corresponding sodium salts **33-37** using the following general procedure for the cyclization of **30**.

The sulfone-ester **30** (1.078 g., 3.0 mmoles) was added in one portion to a stirred solution of sodium methoxide (at 25-30°) prepared by dissolving clean sodium (80 mg., 3.48 eq.) in dry methanol (15.0 ml.). The solution immediately took on a yellow-orange color as the solid began to dissolve. The stirred mixture was refluxed 0.5 hours during which time the color became deep orange and crystalline material separated from the solution. The solution was cooled, filtered and the resulting orange solid was washed with cold methanol and air dried to give **35**·CH_3OH (1.070 g., 94%). Unsolvated **35** was obtained by drying the solvate for 2 hours at 150-160° in high vacuum. Calcd. weight loss: 8.40%. Found: 8.13%; ir (potassium bromide): 1570, 1531, 1240 and 1115 cm^{-1}; nmr (DMSO-d_6): 6.46-8.40 (m, 8H, ArH), 8.46 (s, 1H, H-4). Acidification of a solution of **35** in methanol-water (1:1) gave the conjugate acid **40** in essentially quantitative yield. Two recrystallizations provided pure material; mass spectrum: m/e 327 (M^+), 263 ($M^+ - SO_2$); ir (potassium bromide): 3150 (OH), 1600, 1575, 1295, 1230 and 1103 cm^{-1}; nmr (DMSO-d_6): δ 7.03-8.38 (m, 9H, ArH+OH) 8.91 (s, 1H, quinoline-4H).

Benzyl 2-(3-Carboxyquinolyl) Sulfides (**9** and **11**) and the Corresponding Methyl Esters (**10** and **12**).

The procedure described below for 4-methoxybenzyl 2-(3-carboxyquinolyl) sulfide **11** was also used for the preparation of **9**.

A solution of sodium hydroxide (3.2 g., 80.0 mmoles) in distilled water (25 ml.) was added to a stirred solution of silver nitrate (6.8 g., 40.0 mmoles) in distilled water (175 ml.). The sulfide-aldehyde **8** (5.58 g., 18 mmoles) in tetrahydrofuran (200 ml.) was added and stirring was continued 3 hours. The mixture was then filtered through celite, diluted with water and acidified with acetic acid. The resulting solid was filtered, washed well with water and dried to give essentially pure **11** (5.80 g., 99%). Recrystallization gave pure material which showed the following spectral properties. Mass spectrum: m/e 325 (M^+); ir (potassium bromide): 1680 cm^{-1} (C=O); nmr (DMSO-d_6): δ 3.71 (s, 3H, OCH_3) and 4.48 (s, 2H, CH_2S), 6.86 (d, 2H, J = 8.8 Hz, ArH), 7.31-8.16 (m, 6H, ArH including d, 2H, at δ 7.45, J = 8.8 Hz) and 8.88 (s, 1H, quinoline-4H). The acids **9** (2.90 g., 9.8 mmoles) and **11** (5.0 g., 15.4 mmoles) were esterified with excess diazomethane in chloroform-ether to give the esters **10** (2.93 g., 92%) and **12** (4.60 g., 88%), respectively. Two recrystallizations of **12** gave the analytical sample for which the spectral properties described below were observed; mass spectrum; m/e 339 (M^+); ir (potassium bromide): 1709 cm^{-1} (C=O); nmr (deuteriochloroform): δ 3.75 (s, 3H, OCH_3), 3.96 (s, 3H, OCH_3) and 4.55 (s, 2H, SCH_2), 6.78 (d, 2H, J = 8.8 Hz, ArH), 7.20-8.10 (m, 6H, ArH including d, 2H, at 7.40, J = 8.8 Hz), 8.66 (s, 1H, quinoline-4H).

4-Methoxybenzyl 2-(3-Carbomethoxyquinolyl) Sulfone (**32**) by Oxidation of the Sulfide **12**

To a stirred solution of the sulfide-ester **12** (9.3 g., 27.4 mmoles) in chloroform (350 ml.) was added solid 85% *m*-chloroperbenzoic acid (12.14 g., 60 mmoles) during 0.5 hours while maintaining a temperature range of 25-34°. A second portion of 85% *m*-chloroperbenzoic acid (2.0 g., 9.8 mmoles) was added after 18 hours and stirring was continued for an additional 3 hours. The solution was then washed successively with 10% sodium bisulfite (2 x 100 ml.), 7% sodium bicarbonate (3 x 100 ml.), water (100 ml.) and dried with magnesium sulfate. Evapora-

tion of the solvent gave a solid residue which was recrystallized twice to give pure **32** (4.47 g., 44%); mass spectrum: m/e 371 (M^+); ir (potassium bromide): 1711 cm^{-1} (C=O); nmr (deuteriochloroform): δ 3.71 (s, 3H, OCH_3), 3.98 (s, 3H, OCH_3), 4.90 (s, 2H, SO_2CH_2), 6.78 (d, 2H, J = 8.9 Hz, ArH), 7.35 (d, 2H, J = 8.9 Hz, ArH) 7.50-8.40 (m, 4H, ArH) and 8.55 (s, 1H, quinoline-4H).

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