Preparation and Antiinflammatory Activity of Some 2-Arylbenzo[*b*]thiophen-3(2H)-one 1,1-Dioxides

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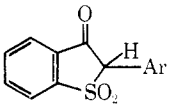
2-Phenylbenzo[*b*]thiophen-3(2H)-one 1,1-dioxide (**1**) was shown to exhibit both anticoagulant and antiinflammatory activity. The latter activity was retained in adrenalectomized rats. Various analogs of **1** were prepared including some which retained antiinflammatory activity, as much as 1.2 times phenylbutazone, but were free of anticoagulant effects.

The successful separation of anticoagulant activity from antiinflammatory activity in a group of 2-aryl-1,3-indandiones[1,2] prompted the preparation of a series of 2-arylbenzo[*b*]thiophen-3(2H)-one 1,1-dioxides. These were evaluated for both anticoagulant (inhibition of prothrombin synthesis) and antiinflammatory (inhibition of carrageenin-induced rat foot edema) activities. After determining that 2-phenylbenzo[*b*]thiophen-3(2H)-one 1,1-dioxide (**1**) exhibited both antiinflammatory and anticoagulant activity, a series of compounds related to **1** was prepared in an effort to

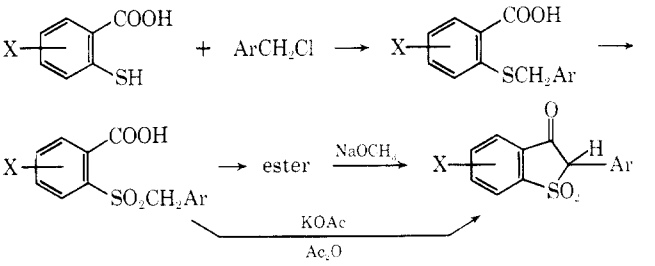


1. Ar = C_6H_5

obtain a useful antiinflammatory agent free of prothrombin effects.

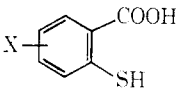
Syntheses.—Although a fairly large variety of benzo[*b*]thiophenes have been made,[3] compounds of this type incorporating all three functional groups, *i.e.*, a 2-aryl group, a 3-oxo function, and a 1,1-dioxide, are somewhat rare. Since the report of Cohen and Smiles[4] who prepared 2-(*p*-aminophenyl)- and 2-(*o*-nitrophenyl)benzo[*b*]thiophen-3(2H)-one 1,1-dioxide and the work of Price and Smiles[5] who reported 2-(*p*-nitrophenyl)-benzo[*b*]thiophen-3(2H)-one 1,1-dioxide, such compounds where these functional groups are combined have received scant attention.[6,7]

In the present work, several synthetic approaches were utilized depending on the accessibility of starting materials. In most instances, an *o*-mercaptobenzoic acid was combined with a benzyl halide in the presence of base to produce an *o*-benzylthiobenzoic acid which was oxidized by H_2O_2 to an *o*-benzylsulfonylbenzoic acid. Cyclization to the desired 2-arylbenzo[*b*]thiophen-3(2H)-one was accomplished either by esterifying the benzoic acid and then treating with NaOMe or by refluxing in Ac_2O containing KOAc.



Where X = H, the procedure of Price and Smiles[5] was also applied for combining *o*-sulfinobenzoic acid with benzyl halides to produce *o*-benzylsulfonylbenzoic acids directly. A closely related procedure involving 3-sulfino-2-naphthoic acid, produced a naphtho[2,3-*b*]-thiophen-3(2H)-one 1,1-dioxide. Previously unreported *o*-mercaptobenzoic acids and substituted benzyl mercaptans prepared in this work are recorded in Tables I and II, respectively (see Experimental Section).

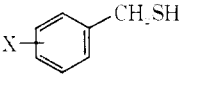
TABLE I
o-MERCAPTOBENZOIC ACIDS



X	Yield, %[a]	Mp, °C	Formula	Analyses or lit. mp, °C
5-CH_3	41	159–161	$C_8H_8O_2S$	C, H
5-Cl	67	192–193		193[b]
4,5-$(CH)_4$	39	273–276		275–276[c]
4,5-$(OCH_3)_2$	50	193–195	$C_9H_{10}O_4S$	C, H

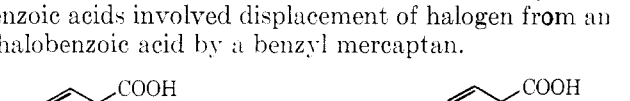
[a] Overall yield for the three-step procedure[12] (diazotization–disulfide formation–Zn reduction) without characterization of intermediates. [b] L. E. Hart, E. W. McClelland, and F. S. Fowkes, *J. Chem. Soc.*, 2114 (1938). [c] German Patent 240,118 to Kalle and Co. (see *Chem. Zentralbl.*, II, 1567 (1911)).

TABLE II
BENZYL MERCAPTANS



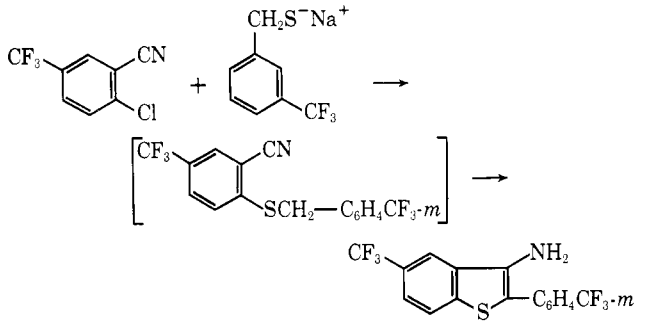
X	Yield, %	Bp, °C (mm)	$n^{25}D$	Formula	Analyses
3-CF_3	61	69–70 (8)	1.4881	$C_8H_7F_3S$	C, H
3-CH_3	67	80–81 (8)	1.5602	$C_8H_{10}S$	C, H
3-Cl	72	118 (19)	1.5830	C_7H_7ClS	C, H

An alternate synthetic approach to the *o*-benzylthiobenzoic acids involved displacement of halogen from an *o*-halobenzoic acid by a benzyl mercaptan.



(1) J. G. Lombardino and E. H. Wiseman, *J. Med. Chem.*, **11**, 342 (1968).
(2) Abstracts of papers of the 154th National Meeting of the American Chemical Society, Chicago, Ill., Sept 12, 1967, Abstract No. P-19.
(3) D. V. Fukushima in "Heterocyclic Compounds," R. C. Elderfield, Ed., John Wiley & Sons, Inc., New York, N. Y., 1951, pp 146–162.
(4) A. Cohen and S. Smiles, *J. Chem. Soc.*, 406 (1930).
(5) W. B. Price and S. Smiles, *ibid.*, 2858 (1928).
(6) O. Dann, German Patent 871,351 (1961) claims 2-phenylbenzo[*b*]-thiophen-3(2H)-one 1,1-dioxide as a fluorescent dye.
(7) A. H. Lamberton and J. E. Thorpe, *J. Chem. Soc., C*, 2571 (1967), prepared 2-(2-naphthyl)benzo[*b*]thiophen-3(2H)-one 1,1-dioxide.

This latter route proved convenient for X = $(CH_3)_2NSO_2$–, and essential when X = CF_3 and Ar = *m*-$CF_3C_6H_4$. Two other 5-trifluoromethyl-2-benzylthiobenzoic acids were conveniently prepared from 4-chloro-3-cyanobenzotrifluoride and appropriate benzyl mercaptans followed by hydrolysis of the resulting 2-benzylthio-5-trifluoromethylbenzonitrile. When the latter approach was applied to *m*-trifluoromethylbenzyl mercaptan, however, no benzonitrile intermediate could be detected by ir analysis. Instead, the only isolable product was 2-(*m*-trifluoromethylphenyl)-5-trifluoromethylbenzo[*b*]thiophene-3-amine.



Apparently, the conjugate base of the intermediate 2-benzylthiobenzonitrile adds to the nitrile function to form the aminobenzo[*b*]thiophene in a manner analogous to the cyclization of *o*-cyanophenylthioglycolic acid to 3-aminobenzo[*b*]thiophene-2-carboxylic acid.[8] The amine was found to resist hydrolysis on prolonged refluxing in NaOH, very likely through formation of the stable conjugate base, preventing further reaction.

Pharmacology.—Antiinflammatory activity was assessed by inhibition of edema formation in the hind paw of the rat (Charles River Strain, average wt 170 g, 6 rats/group) in response to a subplantar injection of carrageenin. The experimental procedure followed that of Winter, *et al.*[9] Edema formation was measured 3 hr after oral administration of test drug (in aqueous solution), and the response of drug-treated animals was compared with that of animals receiving vehicle alone and animals receiving aspirin (100 mg/kg).

Inhibition of prothrombin synthesis was measured in rats by daily oral administration (2 doses) of drug (100 mg/kg in aqueous solution, 4 rats/group) 8 hr apart. Sixteen hours after the last dose, blood samples were drawn into oxalated syringes from the descending aorta while the animals were maintained under light pentobarbital anesthesia. Plasma was separated by centrifugation and prothrombin time determined automatically with a Model 202 clot timer (Mechrolab Inc.) using thromboplastin extract[10] as directed by the manufacturer.

Bilateral adrenalectomy was performed through a retroperitoneal incision, while the rats were maintained under light Et_2O anesthesia. Animals were maintained on a normal diet with 0.9% saline in place of drinking water, and were used 5–7 days postoperatively.

Discussion

2-Phenylbenzo[*b*]thiophen-3(2H)-one 1,-1-dioxide (**1**) was found to be both an anticoagulant and an antiinflammatory agent (Table III). Other 2-arylbenzo[*b*]thiophen-3(2H)-one 1,1-dioxides were made (Table IV) and tested for both types of activities. All compounds unsubstituted at the 5 position (**1–5**) were found to have anticoagulant activity (Table III). Introduction of a 5-methyl substituent (**7–9**), however, removed anticoagulant effects. Combination of 5-chloro with a 2-(*meta*-substituted) aryl group (**11–12**) produced compounds with antiinflammatory activity but free of anticoagulant effects. Other compounds embodying these features include **15**, **22**, **24–27**. With a few exceptions (*e.g.*, **6**, **7**, **8**, **9**, **14**, **19**, **20**), compounds exhibiting antiinflammatory activity fell within an acidity range of 4.8 to 6.2 (acidities determined in 2:1 dioxane–H_2O). The most potent antiinflammatory activity was seen with compounds having a 5-trifluoromethyl substituent (*i.e.*, **25**, **26**). Comparing dose–response curves for **25** and phenylbutazone in the rat foot edema test indicated a relative potency of 1.24.

TABLE III
PHARMACOLOGICAL ACTIVITY OF 2-ARYLBENZO[b]THIOPHENE-3(2H)-ONE 1,1-DIOXIDES

No.	pK_a[a]	Anti-inflammatory[b] activity	Prothrombin[c] effects
1	6.2	+[d]	++
2	5.6	+	++
3	5.2	+[d]	++
4	4.6	+	++
5		−	++
6	5.3	−	*e*
7	6.6	−	−
8	5.5	−	−
9	4.9	−	−
10	5.5	+	++
11	4.3	+	−
12	3.8	+	−
13	4.8	+	++
14	5.7	−	−
15	4.9	+[d]	−
16	5.2	+	−
17	4.8	+	−
18	3.5	−	−
19	4.7	−	−
20	3.8	−	−
21	7.5	−	−
22	6.4	+	−
23	6.9	−	−
24	4.3	+	−
25	5.0	+++[d]	−
26	5.2	++[d]	−
27	4.1	+	−
Phenylbutazone	6.4	+++	−

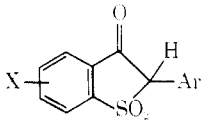
[a] Potentiometric titrations in 2:1 dioxane–H_2O. [b] Antiinflammatory activity is reported as a mean inhibition of edema in the treated animals within the range of 0.5–1.5 times that of the mean inhibition of concurrently treated animals receiving aspirin (100 mg/kg p. o.); +, drug given at 100 mg/kg; ++, drug given at 33 mg/kg; +++, drug given at 10 mg/kg p. o. Compounds with antiinflammatory activity (at 100 mg/kg) of less than 0.5 times aspirin are reported as −. [c] +, prolongation of prothrombin time 16 hr after administration of 9 oral doses, 8 hr apart (100 mg/kg p. o.); ++, prolongation of prothrombin time 16 hr after administration of 2 oral doses, 8 hr apart (100 mg/kg p. o.); −, no prolongation of prothrombin time after 9 oral doses, 8 hr apart (100 mg/kg p. o.). [d] A similar antiinflammatory response was obtained with these compounds in both adrenalectomized and nonadrenalectomized rats dosed at 100 mg/kg p.o. [e] Not measured due to insufficient supplies of compound.

(8) C. E. Dalgliesh and F. G. Mann, *J. Chem. Soc.*, 893 (1945).

(9) (a) C. A. Winter, E. A. Risley, and G. W. Nuss, *Proc. Soc. Exp. Biol. Med.*, **111**, 544 (1962); (b) *J. Pharmacol. Exp. Therap.*, **141**, 369 (1963).

(10) Simplastin®, Warner–Chilcott.

TABLE IV
2-ARYLBENZO[*b*]THIOPHENE-3(2H)-ONE 1,1-DIOXIDES



No.	X	Ar	Yield, %	Method of prepn[a]	Mp, °C	Crystn solvent[b]	Formula	Analyses
1	H	C_6H_5	61		176–178[c]			
2	H	4-ClC_6H_4	60	A	147–149	E	$C_{14}H_9ClO_3S$	C, H
3	H	3-$CF_3C_6H_4$	56	A	142–144	E	$C_{15}H_9F_3O_3S$	C, H
4	H	3-$NO_2C_6H_4$	32	A	218–220	E	$C_{14}H_9NO_5S$	C, H, N
5	H	1-Naphthyl	24	A	162–166	I	$C_{18}H_{12}O_3S$	C, H
6	H	C_6F_5	92	B	132–133	E	$C_{14}H_5F_5O_3S$	C, H
7	5-CH_3	C_6H_5	71	A	184–186	E	$C_{15}H_{12}O_3S$	C, H
8	5-CH_3	3-$CF_3C_6H_4$	95	C	146–148	E	$C_{16}H_{11}F_3O_3S$	C, H
9	5-CH_3	3-$NO_2C_6H_4$	38	A	213–215	E	$C_{15}H_{11}NO_5S$	C, H, N
10	5-Cl	C_6H_5	89	C	181–183	E	$C_{14}H_9ClO_3S$	C, H
11	5-Cl	3-$CF_3C_6H_4$	93	C	161–163	E	$C_{15}H_8ClF_3O_3S$	C, H
12	5-Cl	3-$NO_2C_6H_4$	88	C	215–216	E	$C_{14}H_8ClNO_5S$	C, H, N
13	5-Cl	4-ClC_6H_4	84	C	158–161	E	$C_{14}H_8Cl_2O_3S$	C, H
14	5,6-$(CH)_4$	C_6H_5	42	D	170–173	E	$C_{18}H_{12}O_3S$	C, H
15	5,6-$(CH)_4$	3-$CF_3C_6H_4$	41	D	188–189	E	$C_{19}H_{11}F_3O_3S$	C, H
16	5,6-$(CH)_4$	4-ClC_6H_4	23	D	235–237	E	$C_{18}H_{11}ClO_3S$	C, H
17	5-$(CH_3)_2NSO_2$	C_6H_5	55	C	189–191	E	$C_{16}H_{15}NO_5S_2$	C, H, N
18	5-$(CH_3)_2NSO_2$	3-$CF_3C_6H_4$	75	B	171–173	E	$C_{17}H_{14}F_3NO_5S_2$	C, H, N
19	5-$(CH_3)_2NSO_2$	3-$CH_3C_6H_4$	35	B	158–160	M–W	$C_{17}H_{17}NO_5S_2$	C, H, N
20	5-$(CH_3)_2NSO_2$	3-ClC_6H_4	36	B	187–189	E	$C_{16}H_{14}ClNO_5S_2$	C, H, N
21	5,6-$(OCH_3)_2$	C_6H_5	50	C	220–222	E	$C_{16}H_{14}ClO_5S$	C, H
22	5,6-$(OCH_3)_2$	3-$CF_3C_6H_4$	86	C	201–202	E	$C_{17}H_{13}F_3O_5S$	C, H
23	5,6-$(OCH_3)_2$	4-ClC_6H_4	81	C	225–228	E	$C_{16}H_{14}ClO_5S$	C, H
24	5-NO_2	3-$CH_3C_6H_4$	45	B	140–142	E	$C_{15}H_{11}NO_5S$	C, H, N
25	5-CF_3	C_6H_5	83	C	197–198		$C_{15}H_9F_3O_3S$	C, H
26	5-CF_3	3-$CH_3C_6H_4$	79	C	176–178	E	$C_{16}H_{11}F_3O_3S$	C, H
27	5-CF_3	3-$CF_3C_6H_4$	83	C	198–199		$C_{16}H_8F_6O_3S$	C, H

[a] A = Prepared by esterification of an *o*-benzylsulfonylbenzoic acid followed by base-catalyzed cyclization as illustrated in the Experimental Section for **2**. B = cyclization of an *o*-benzylsulfonylbenzoic by Ac_2O–KOAc as illustrated for **18**. C = esterified an *o*-benzylsulfonylbenzoic acid *via* the acid chloride and then cyclized as illustrated for **8**. D = see Experimental Section. [b] E = EtOH; I = *i*-PrOH; M = MeOH; W = H_2O. Absence of any symbol indicates the compound was obtained analytically pure by thorough trituration with H_2O. [c] Reference 4 reports mp 174°.

Experimental Section[11]

Substituted *o*-Mercaptobenzoic Acids.—The required *o*-mercaptobenzoic acids (Table I) were prepared from commercially available anthranilic acids by the method of Allen and MacKay.[12] Dimethoxyanthranilic acid was made by the method of Zincke and Francke[13] *via* nitration of veratric acid Me ester followed by reduction of NO_2 and hydrolysis of the ester function.

Substituted Benzyl Mercaptans.—The required benzyl mercaptans (Table II) were prepared from commercially available benzyl chlorides *via* the isothiouronium salt essentially by the procedure of Urquhart, *et al.*[14] After acidification, the products were extracted (Et_2O), dried, and vacuum distilled.

α-Chloro-*m*-xylene and α,*m*-dichlorotoluene were purchased from the Aldrich Chemical Co. *m*-Trifluoromethylbenzyl chloride and pentafluorobenzyl bromide were purchased from Pierce Chemical Co. and *m*-nitro- and *p*-chlorobenzyl chloride were Eastman Organic Chemicals.

2-(*p*-Chlorophenyl)benzo[*b*]thiophen-3(2H)-one 1,1-Dioxide (2).—A solution of 10.0 g (0.032 mol) of **55** in 400 ml of absolute EtOH was saturated with dry HCl and refluxed for 24 hr. Evaporation to dryness gave a light yellow oil which was partitioned between 10% $NaHCO_3$–Et_2O. The Et_2O layer was washed with H_2O and dried (Na_2SO_4). Removal of all solvent yielded a viscous oil which was dissolved in 200 ml of 0.5 *M* NaOEt–EtOH. After refluxing for 2 hr, concentration to dryness gave a yellow solid which was dissolved in 300 ml of H_2O and acidified with 6 *N* HCl to yield 5.6 g (60%) of **2**, mp 145–148° (Table IV). A sample was recrystallized from EtOH for analysis, mp 147–149°.

5-Methyl-2-(*m*-trifluoromethylphenyl)benzo[*b*]thiophen-3(2H)-one 1,1-Dioxide (8).—After refluxing a solution of 8.0 g (0.022 mol) of **60** in 50 ml of C_6H_6 and 50 ml of $SOCl_2$ for 1 hr, evaporation to dryness (reduced pressure) gave a white solid. The resulting residue was suspended in 50 ml of MeOH and refluxed for 1 hr producing a yellow solution which was evaporated to dryness to yield a pale yellow solid. This residue was suspended in 200 ml of absolute EtOH and 90 ml of 1 *M* NaOEt in EtOH added. Refluxing for 1.5 hr and removal of all solvent produced a yellow solid which was dissolved in 500 ml of H_2O and acidified (6 *N* HCl) to yield 7.2 g (95%) of **8**, mp 142–145°. Recrystallization from EtOH gave mp 146–148°.

2-Phenylnaphtho[2,3-*b*]thiophen-3(2H)-one 1,1-Dioxide (14).—Oxidation of 1.7 g (0.0058 mol) of 3-benzylthio-2-naphthoic acid (**40**) was carried out using H_2O_2 in HCOOH as illustrated below for **55**. The resulting crude, tan solid (1.5 g) was refluxed with 30 ml of $SOCl_2$ and 30 ml of C_6H_6 for 1 hr. After evaporating to dryness, 50 ml of MeOH was added and the solution refluxed for 0.5 hr. After evaporation to dryness, the residue was com-

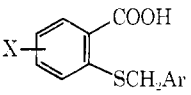
(11) Melting points were determined in a Thomas–Hoover capillary melting point apparatus using a calibrated thermometer and are uncorrected. Potentiometric titrations were carried out in 2:1 dioxane–H_2O (v/v) solvent using a Beckman Model G pH meter and standard 0.5 *N* NaOH. The apparent pK_a values correspond to the pH values at the half-neutralization point in these titrations. A Varian A-60 spectrometer (Me_4Si standard) was used to measure nmr spectra. Ir spectra were determined in KBr pellets. Analyses were carried out by the Physical Measurements Laboratory of Chas. Pfizer & Co., Inc. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements are within ±0.4% of the theoretical values.

(12) C. F. H. Allen and D. D. MacKay, "Organic Syntheses," Coll. Vol. II, A. H. Blatt, Ed., John Wiley & Sons, Inc., New York, N. Y., 1943, p 580.

(13) T. Zincke and B. Francke, *Ann. Chem.*, **293**, 189 (1896).

(14) G. G. Urquhart, J. W. Gates, Jr., and R. Connor in "Organic Syntheses," Coll. Vol. III, E. C. Horning, Ed., John Wiley & Sons, Inc., New York, N. Y., 1955, p 363.

TABLE V
o-BENZYLTHIOBENZOIC ACIDS



No.	X	Ar	Yield, %	Method of prepn.[a]	Mp, °C	Crystn solvent[b]	Formula	Analyses
28	H	C_6H_5	98		187–189[c]			
29	H	4-ClC_6H_4	86	A	218–219	I	$C_{14}H_{11}ClO_2S$	C, H
30	H	3-$CF_3C_6H_4$	90	A	151–153	E	$C_{15}H_{11}F_3O_2S$	C, H
31	H	3-$NO_2C_6H_4$	97	A	192–194	E	$C_{14}H_{11}NO_4S$	C, H, N
32	H	1-Naphthyl	97	A	179–181	E	$C_{18}H_{14}O_2S$	C, H
33	5-CH_3	C_6H_5	89	A	169–171		$C_{15}H_{14}O_2S$	C, H
34	5-CH_3	3-$CF_3C_6H_4$	96	A	153–155		$C_{16}H_{13}F_3O_2S$	C, H
35	5-CH_3	3-$NO_2C_6H_4$	95	A	164–167		$C_{15}H_{13}NO_4S$	C, H, N
36	5-Cl	C_6H_5	69	A	184–185	Et–H	$C_{14}H_{11}ClO_2S$	C, H
37	5-Cl	3-$CF_3C_6H_4$	71	A	165–167	Et–H	$C_{15}H_{10}ClF_3O_2S$	C, H
38	5-Cl	3-$NO_2C_6H_4$	76	A	174–176	E	$C_{14}H_{10}ClNO_4S$	C, H, N
39	5-Cl	4-ClC_6H_4	67	A	178–180	Et–H	$C_{14}H_{10}Cl_2O_2S$	C, H
40	4,5-$(CH)_4$	C_6H_5	94	A	247–249	M	$C_{18}H_{14}O_2S$	C, H
41	4,5-$(CH)_4$	3-$CF_3C_6H_4$	70	A	222–225	E–W	$C_{19}H_{13}F_3O_2S$	C, H
42	4,5-$(CH)_4$	4-ClC_6H_4	48	A	218–221	E	$C_{18}H_{13}ClO_2S$	C, H
43	5-$(CH_3)_2NSO_2$	C_6H_5	69[d]	B	224–225	A	$C_{16}H_{17}NO_4S_2$	C, H, N
44	5-$(CH_3)_2NSO_2$	3-$CF_3C_6H_4$	79	B	207–210	E–W	$C_{17}H_{16}F_3NO_4S_2$	C, H, N
45	5-$(CH_3)_2NSO_2$	3-$CH_3C_6H_4$	81	B	215–217	E	$C_{17}H_{19}NO_4S_2$	C, H, N
46	5-$(CH_3)_2NSO_2$	3-ClC_6H_4	77	B	211–212	E	$C_{16}H_{16}ClNO_4S_2$	C, H, N
47	4,5-$(OCH_3)_2$	C_6H_5	96	A	176–176.5		$C_{16}H_{16}O_4S$	C, H
48	4,5-$(OCH_3)_2$	3-$CF_3C_6H_4$	98	A	185–187		$C_{17}H_{15}F_3O_4S$	C, H
49	4,5-$(OCH_3)_2$	4-ClC_6H_4	97	A	183–184		$C_{16}H_{15}ClO_4S$	C, H
50	5-NO_2	3-$CH_3C_6H_4$	38	B[e]	238–240	E	$C_{15}H_{13}NO_4S$	C, H, N
51	5-CF_3	C_6H_5	84	C	180–181	B	$C_{15}H_{11}F_3O_2S$	C, H
52	5-CF_3	3-$CH_3C_6H_4$	80	C	192–195		$C_{16}H_{13}F_3O_2S$	C, H
53	5-CF_3	3-$CF_3C_6H_4$	55	C	165–166	Et–H	$C_{16}H_{10}F_6O_2S$	C, H

[a] A = An *o*-mercaptobenzoic acid was treated with a $PhCH_2Cl$ as illustrated in the Experimental Section for **29**. B: an *o*-bromo- (or chloro-) benzoic acid was treated with a $PhCH_2SH$ as illustrated for **44**. C: see Experimental Section. [b] E = EtOH; W = H_2O; M = MeOH; Et = Et_2O; H = hexane; B = C_6H_6; A = MeCN; I = *i*-PrOH. [c] H. Apitzsch, *Ber.*, **46**, 3102 (1913), reports mp 189°. [d] Kindly provided by Dr. Richard Koch of these laboratories. [e] Using 2-chloro-5-nitrobenzoic acid (Aldrich Chemical Co.) as starting material.

bined with 0.76 g (0.014 mol) of $NaOCH_3$ and 25 ml of MeOH and refluxed for 0.5 hr. Addition of 150 ml of H_2O followed by acidification (6 *N* HCl) produced a tan solid which, after recrystallization from EtOH, gave 0.59 g (42%) of **14** (see Table IV).

By identical procedures **15** and **16** were produced from **41** and **42**, respectively, *via* the crude sulfones followed by base-catalyzed cyclization.

A superior technique for preparing **2-(*m*-trifluoromethylphenyl)naphtho[2,3-*b*]thiophen-3(2H)-one 1,1-dioxide (15)** is as follows. To 11.8 g (0.050 mol) of 3-sulfino-2-naphthoic acid (see below), 10.2 g (0.10 mol) of Et_3N, and 100 ml of MeCN was added 19.5 g (0.10 mol) of *m*-trifluoromethylbenzyl chloride. After refluxing for 16 hr, $Et_3N \cdot HCl$ was filtered, the filtrate was concentrated to an oil which was crystallized from MeOH to give 12.9 g (47%) of **3-(*m*-trifluoromethylbenzyl)sulfonyl-2-naphthoic acid *m*-trifluoromethylbenzyl ester,** mp 111–112.5°. *Anal.* ($C_{27}H_{18}F_6O_4S$) C, H. A solution of 18 g (0.33 mol) of $NaOCH_3$ in 560 ml of MeOH was stirred at 40° as 62 g (0.112 mol) of the above ester was added over 10 min. After refluxing the solution for 1 hr, evaporation yielded a semisolid which was diluted with 120 ml of H_2O, cooled, and acidified (12 *N* HCl). The resulting slurry was extracted ($CHCl_3$) and the extracts were dried (Na_2SO_4) and evaporated. Recrystallization from EtOH gave 36 g (81%) of **15**, mp 191–192°; nmr ($CDCl_3$): τ 4.66 (s, 1, 2-H), 1.70–2.4 (m, 8, aromatic protons), 1.42 (s, 1, 9-H), 1.30 (s, 1, 4-H).

2-(*m*-Trifluoromethylphenyl)benzo[*b*]thiophen-3(2H)-one 1,1-Dioxide (18).—After refluxing a solution of 6.8 g (0.015 mol) of **67** in 150 ml of Ac_2O containing 0.10 g of anhydrous KOAc for 3.5 hr, concentration to dryness under reduced pressure gave a yellow oil. Brief refluxing of a solution of this oil in 100 ml of EtOH and 100 ml of 5% NaOH following by concentration to 100 ml gave a yellow suspension. Addition of 300 ml of H_2O and then acidification with 6 *N* HCl produced a yellow solid which, after recrystallization from EtOH, yielded 4.9 g, (75%) of **18** (Table IV).

2-(*p*-Chlorobenzylthio)benzoic Acid (29).—A combination of 15.4 g (0.10 mol) of *o*-mercaptobenzoic acid, 16.1 g (0.10 mol) of *p*-chlorobenzyl chloride, 13.8 g (0.10 mol) of K_2CO_3, 250 ml of EtOH, and 125 ml of H_2O was refluxed for 2 hr. Acidification with 6 *N* HCl precipitated a white solid which, after thorough trituration with H_2O, gave 23.9 g (86%) of **29** (see Table V).

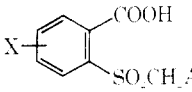
2-(*m*-Trifluoromethylbenzylthio)-5-dimethylsulfamoylbenzoic Acid (44).—A suspension of 9.2 g (0.030 mol) of 2-bromo-5-dimethylsulfamoylbenzoic acid,[15] 6.2 g (0.032 mol) of *m*-trifluoromethylbenzyl mercaptan, 4.0 g of KOH, 90 mg of Cu powder, and 150 ml of DMF was heated at 125° for 19 hr. After filtration and evaporation to dryness under vacuum, the residue was dissolved in 400 ml of H_2O and acidified (6 *N* HCl) to produce a gum which slowly crystallized on stirring in the cold. Recrystallization from EtOH–H_2O gave 9.9 g (79%) of **44** (Table V).

2-Benzylthio-5-trifluoromethylbenzoic Acid (51).—A solution of 13.4 g (0.11 mol) of benzyl mercaptan, 50 ml of DMF, and 5.9 g (0.11 mol) of NaOMe was cooled to 15° and then added over 0.5 hr to a solution of 23 g (0.11 mol) of 4-chloro-3-cyanobenzotrifluoride (Pierce Chemical Co.) in 30 ml of DMF. After stirring 1.5 hr at room temperature, the mixture was added to 800 ml of cold H_2O and extracted with $CHCl_3$. After drying, removal of solvent yielded 34 g of a pale yellow oil, presumably 2-benzylthio-5-trifluoromethylbenzonitrile. A combination of 17.5 g (0.06 mol) of this crude nitrile, 50 ml of EtOH, and 200 ml of 20% NaOH was refluxed for 24 hr. Concentration of the reaction under reduced pressure followed by Et_2O extraction yielded, on removal of the ether, a pale orange oil. Suspending the oil in H_2O and acidifying with 6 *N* HCl produced a white solid, 15.7 g (84%) of **51** which was purified for analysis by recrystallization (C_6H_6) (Table V).

By essentially the same procedure, except for employing *m*-methylbenzyl mercaptan in place of benzyl mercaptan, an 80% yield of **52** was realized. When an attempt was made to prepare

(15) B. M. Bloom and J. F. Muren, U. S. Patent 3,310,553 (1967).

TABLE VI
o-BENZYLSULFONYLBENZOIC ACIDS



No.	X	Ar	Yield, %	Method of prepn.[a]	Mp, °C	Crystn. solvent[b]	Formula	Analyses
54	H	C_6H_5		A	131–134[c]			
55	H	4-ClC_6H_4	98	A	187–189	E	$C_{14}H_{11}ClO_4S$	C, H
56	H	3-$CF_3C_6H_4$	84	A	128–130	Et–H	$C_{15}H_{11}F_3O_4S$	C, H
57	H	3-$NO_2C_6H_4$	84	A	239–241		$C_{14}H_{11}NO_6S$	C, H, N
58	H	C_6F_5	58	B	172–176	E–W	$C_{14}H_7F_5O_4S$	C, H
59	5-CH_3	C_6H_5	91	B	198–201	E	$C_{15}H_{14}O_4S$	C, H
60	5-CH_3	3-$CF_3C_6H_4$	96	A	156–159		$C_{16}H_{13}F_3O_4S$	C, H
61	5-CH_3	3-$NO_2C_6H_4$	83	A	213–216		$C_{15}H_{13}NO_6S$	C, H, N
62	5-Cl	C_6H_5	83	A	180–181	Et–H	$C_{14}H_{11}ClO_4S$	C, H
63	5-Cl	3-$CF_3C_6H_4$	91	A	149–152	E–W	$C_{15}H_{10}ClF_3O_4S$	C, H
64	5-Cl	3-$NO_2C_6H_4$	93	A	179–181	E	$C_{14}H_{10}ClNO_6S$	C, H, N
65	5-Cl	4-ClC_6H_4	80	A	167–170	Et–H	$C_{14}H_{10}Cl_2O_4S$	C, H
66	5-$(CH_3)_2NSO_2$	C_6H_5	61[d]	C	225–226	EAc	$C_{16}H_{17}NO_6S_2$	C, H, N
67	5-$(CH_3)_2NSO_2$	3-$CF_3C_6H_4$	89	C	198–200		$C_{17}H_{16}F_3NO_6S_2$	C, H, N
68	5-$(CH_3)_2NSO_2$	3-$CH_3C_6H_4$	87	C	222–224		$C_{17}H_{19}NO_6S_2$	C, H, N
69	5-$(CH_3)_2NSO_2$	3-ClC_6H_4	70	C	207–210	E–W	$C_{16}H_{16}ClNO_6S_2$	C, H, N
70	4,5-$(OCH_3)_2$	C_6H_5	86	A	196–197		$C_{16}H_{16}O_6S$	C, H
71	4,5-$(OCH_3)_2$	3-$CF_3C_6H_4$	95	A	206–207		$C_{17}H_{15}F_3O_6S$	C, H
72	4,5-$(OCH_3)_2$	4-ClC_6H_4	88	A	197–198		$C_{16}H_{15}ClO_6S$	C, H
73	5-NO_2	3-$CH_3C_6H_4$	88	C	244–246		$C_{15}H_{13}NO_6S$	C, H, N
74	5-CF_3	C_6H_5	73	A	171–172		$C_{15}H_{11}F_3O_4S$	C, H
75	5-CF_3	3-$CH_3C_6H_4$	80	A	165–166	E–W	$C_{16}H_{13}F_3O_4S$	C, H
76	5-CF_3	3-$CF_3C_6H_4$	80[16]	C	192–193	Et–H	$C_{16}H_{10}F_6O_4S$	C, H

[a] A = Oxidation of the sulfide in HCO_2H–H_2O_2 as illustrated in the Experimental Section for **55**. B = see Experimental Section; C = oxidation of the sulfide in AcOH–H_2O_2. [b] E = EtOH; Et = Et_2O; H = hexane; W = H_2O; EAc = EtOAc. Absence of any symbol indicates the compound was obtained analytically pure by thorough trituration with H_2O. [c] Reference 4 gives mp 126–128°. [d] Kindly provided by Dr. Richard Koch of these laboratories.

53 by the above procedure, except employing *m*-trifluoromethylbenzyl mercaptan, the following results were obtained:

2-(*m*-Trifluoromethylphenyl)-5-trifluoromethylbenzo[*b*]thiophene-3-amine.—The Na salt of *m*-trifluoromethylbenzyl mercaptan was prepared under N_2 from 5.7 g (0.03 mol) of the mercaptan in 35 ml of MeOH containing 30 ml of 1 *M* NaOMe–MeOH. Removal of all solvent under reduced pressure yielded a white solid. Addition of 50 ml of DMF and 6.2 g (0.030 mol) of 4-chloro-3-cyanobenzotrifluoride gave a red solution which was heated (steam bath) for 1 hr. After pouring into 300 ml of cold H_2O, extraction (Et_2O) and removal of all solvent produced a yellow oil, 10.5 g (97%), which slowly crystallized; no nitrile absorption near 4.5 μ. A solution of this crude soft solid in EtOH (100 ml) and 20% NaOH (100 ml) produced two layers when refluxed for 2 days. The upper layer was separated and evaporated, and the residue suspended in H_2O and acidified to give a white solid, mp 92–95°, identical on silica gel tlc plates (isooctane–10% HOAc, 2 passes) with the crude soft solid employed as starting material for this hydrolysis. Ir spectra (see below) of the two materials were essentially identical. Recrystallization from EtOH–H_2O gave a solid, mp 100–102°. *Anal.* ($C_{16}H_9F_6NS$) C, H, N. Nmr ($CDCl_3$): τ 2.0–2.5 (m, 7, aromatic protons), 5.9 (s, broad, 2, NH_2, exchanges with D_2O); uv max (EtOH) 271 mμ (12,000), 345 (7880); ir 2.92 and 2.99 (NH_2) (no other bands below 6.0), and 7.5 μ (CF_3).

2-(*m*-Trifluoromethylbenzylthio)-5-trifluoromethylbenzoic Acid (53).[16]—A solution of 22.5 g (0.11 mol) of 2-chloro-5-trifluoromethylbenzoic acid,[17] 16 g (0.10 mol) of *m*-trifluoromethylbenzyl mercaptan, and 10.8 g (0.20 mol) of NaOMe in 200 ml of DMF was heated at 90° for 6 hr. After cooling to room temperature, addition to a solution of 800 ml of H_2O and 20 ml of 12 *N* HCl produced a solid which was extracted (Et_2O). After drying, evaporation of all solvent gave a soft residue which was slurried in hexane to yield 21 g (55%) of **53** (Table V).

2-(*p*-Chlorobenzylsulfonyl)benzoic Acid (55).—To a suspension of 15.0 g (0.054 mol) of **29** in 300 ml of 97% HCOOH warmed to 55° was slowly added 20 ml of 30% H_2O_2. The resulting tan solution was kept at 55° for 3 hr and then allowed to stand overnight at room temperature. After removal of all solvent at reduced pressure, a white solid residue resulted, 16.4 g (98%) of **55** (Table VI), mp 187–189° after recrystallization from EtOH.

2-(Pentafluorobenzylsulfonyl)benzoic Acid (58).—To a solution of 3.5 g (0.019 mol) of *o*-sulfinobenzoic acid,[3] 350 ml of MeOH and 38 ml of 1 *M* $NaOCH_3$ in MeOH was added 5.0 g (0.019 mol) of pentafluorobenzyl bromide. After refluxing for 3 hr, the reaction was concentrated to half-volume under reduced pressure, an equal volume of H_2O added, and the solution acidified to produce 4.0 g (58%) of **58** (see Table VI).

3-Sulfino-2-naphthoic Acid.—A suspension of 44.9 g (0.24 mol) of 3-amino-2-naphthoic acid, 360 ml of H_2O, 600 ml of THF, and 120 ml of H_2SO_4 was cooled to 2°. Addition of 18.2 g (0.264 mol) of $NaNO_2$ in 300 ml of H_2O was regulated to keep the reaction below 5°. Upon complete addition, SO_2 was bubbled rapidly through the solution while maintaining the temperature below 7°. After 15 min, and while continuing SO_2 addition, 60 g of Cu powder was added. After 1 hr of SO_2 addition at 5°, the reaction was stirred for 1 hr at room temperature. Filtration of the Cu and evaporation of THF yielded a dark tar, which crystallized upon trituration successively with $CHCl_3$ and then Et_2O producing 38.6 g (68%) of pale gray solid, mp 144–145° dec. *Anal.* ($C_{11}H_8O_4S$) C, H.

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(16) This experiment was carried out by Dr. G. F. Holland of these laboratories.

(17) G. Saucy and L. H. Sternbach, *Helv. Chim. Acta*, **45**, 2233 (1962).