Biologically Oriented Organic Sulfur Chemistry. 14. Antiinflammatory Properties of Some Aryl Sulfides, Sulfoxides, and Sulfones[1]

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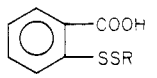
To extend earlier work, to examine the possibility that certain sulfoxides might serve as counterparts of amines in receptor-site interactions, and to add to the little information available about sulfoxides in medicinal chemistry, sulfoxides were prepared of the general structure $XArS(O)C_6H_4(CHR)_nCO_2H$, together with the sulfides and some of the sulfones. The products were evaluated as antiinflammatory agents by carrageenan-edema inhibition and uv-erythema inhibition. Four of the compounds had activity roughly comparable to aspirin or phenylbutazone in one or the other of these assays (**2a–c**, **3b**). Sulfoxides did not seem especially promising as a class and usually were less active than the corresponding sulfides. The two most interesting compounds in these assays, *o*-(phenylthio)phenylacetic acid (**2b**) and its sulfoxide **3b**, had no significant activity in adjuvant arthritis. Hydrogen-bonding effects are indicated in certain of the acids by their absence in the corresponding esters.

Previous work indicated antiinflammatory activity for compounds of structure **1**,[3] compound **1a** showing 40% inhibition of carrageenan-induced edema in mice at a dose of 30 mg/kg.[3] Certain of the variants of **1** reported without activities earlier in another connection[3] also had sufficient



1 (**1a**, R = $CH_2CH_2NH_2$)

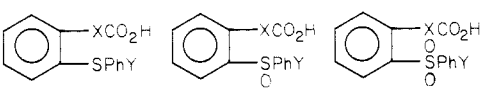
activity to encourage further scrutiny of congeners [R of **1** and percent inhibition of carrageenan-induced edema in the hind paw of rats given 50 mg/kg po × 2, with much the same procedure described below, were DL-$CMe_2CH(NHAc)CO_2H$, 24; Ph, 21; *n*-Bu, 17 (25 mg/kg × 2); L-$CH_2CH(NH_2)CO_2H$, 9; and D-$CMe_2CH(NH_2)CO_2H$, 0].

Contraction of the –SS– moiety of **1** to –S– would be one desirable modification of **1**, since it should lend a structural similarity to the active class of fenamates (substituted *o*-arylaminobenzoic acids). Introduction of a methylene or substituted methylene moiety between the ring and carboxyl group of **1** would be another, since this change should confer some similarity to the active class of aryl aliphatic carboxylic acids.

While we were considering diphenyl sulfides that would embody such changes, the possibility struck us that sulfoxide functions, –S(O)–, afforded a second reason for interest in such series because at receptor sites they might usefully simulate amine functions, –NR–, perhaps lending further similarity to the fenamates. If –S(O)– did indeed lead to receptor-site behavior resembling in some ways that of amine functions, but differing in other ways (e.g., those producing adverse drug effects), the frequent occurrence of amine functions in drugs could make such behavior useful generally in medicinal chemistry. Several facts suggested that –S(O)– might share certain receptor-site characteristics of amines but to usefully different extents. (1) Sulfoxides are slightly basic; they are more soluble in aqueous acid than in water, and treatment with hydrochloric or nitric acid can give isolable salts from which sulfoxides can be regenerated.[4] Although the basicities of sulfoxides seem more comparable to those of phosphine oxides, pyridine oxide, and *N,N*-dimethylacetamide (while greater than those of ketones),[5a] than to those of amines, –S(O)– moieties might simulate amine basicities enough to afford receptor-site interactions. (2) The configurational aspects of sulfoxides resemble those of ammonium salts in that both classes are resolvable.[5b] (3) Space-filling models of the moieties $MeS(O)CH_2$– and Me_2NCH_2– are quite similar in size, with unshared electron pairs being in apparently similar tetrahedrally disposed relationships. (4) Sulfoxides are well known to react with alkyl halides to give oxosulfonium salts, i.e., $R_3S^+(O)X^-$, in reactions reminiscent of those of amines to give ammonium salts and thus reflect a nucleophilicity reminiscent of amines. (5) Studies of unsymmetrical disulfides indicate that both NH_2 groups[6] and sulfinate groups ($-SO_2^-$)[7] accelerate disproportionation, perhaps indicating intramolecular involvement of unshared electron pairs.

A third incentive for studying such series is the relatively slight information that has been reported about sulfoxides in medicinal chemistry, one notable exception being sulfinpyrazone.[8] This paucity of application is surprising when one considers the wide variety of pharmacological activities attributed to dimethyl sulfoxide.[9a]

Chemistry. The three factors outlined (viz. the desirability of further modifications of **1**, the possible similarity of sulfoxide and amine functions, and the need for information about sulfoxides) led us to prepare compounds of structures **2** and **3** for evaluation as antiinflammatory agents. The sulfides **2** were of interest per se and also



2 **3** **4**

	X	Y
a		H
b	CH_2	H
c		3-CF_3
d		2,3-$(CH_3)_2$
e	$CH(CH_3)$	H

afforded a reference point for noting any marked differences attributable to sulfoxide functions in **3**. Sulfones usually have little in common with sulfides or sulfoxides, but several (**4**) were prepared to help complete the picture (the sulfones **4b** and **4e** were not prepared). So far as analogy to fenamates is concerned, there may be some basis for pessimism, since replacement of –NH– by –S– or $-SO_2$– in similar (but unspecified) systems seems not to have been fruitful for antierythemic activity;[9b] too, exchange of –S(O)– for the –NH– of fenamates may not provide a good test for whether –S(O)– can indeed usefully simulate $-N(CH_3)$–, since N-methylation of fenamic acid reduces both antierythemic and antiedemic activity.[9b] Table I shows the properties of the sulfides **2**, sulfoxides **3**, and sulfones **4** prepared.

2-(Phenylthio)benzoic acid (**2a**) was prepared at first by the procedure of Weedon and Doughty, i.e., by diazotization of anthranilic acid followed by coupling with sodium thiophenate,[10] but with the modifications of catalysis by copper powder and of coupling at 0° instead of at 50° (caution: see Experimental Section). However, we later found that **2a** is obtained in higher yield and purity by the

Table I. Antiinflammatory Properties of Sulfides 2, Sulfoxides 3, and Sulfones 4

Compd	Structure	Procedure[a]	Recrystn solvent[b]	Mp, °C	Yield, %[c]	Formula	Analyses[d]	Carrageenan edema, % inhibn[e]	Uv erythema, % inhibn[f]
2a	2-(PhS)$C_6H_4CO_2H$	A-1	E-W	168-171	61	*g*	*g*	31	11
		A-2	E-W	169-171	82	*g*	*g*		
		A-3	E-W	168.5-171	88	*g*	*g*		
2b	2-(PhS)$C_6H_4CH_2CO_2H$	*c*	E-W, EA	121-122	61[c]	$C_{14}H_{12}O_2S$[g]	C, H, S	23	51
2c	2-(3'-F_3CPhS)$C_6H_4CO_2H$	A-3	E-W	147.5-149	92	$C_{14}H_9F_3O_3S$[g]	C, H, F, S	18	43[h]
2d	2-[2',3'-$(CH_3)_2$PhS]$C_6H_4CO_2H$	A-3	D-W	244-246	82	$C_{15}H_{14}O_2S$	C, H, S	15	26
2e	2-(PhS)$C_6H_4CH(CH_3)CO_2H$	*c*	H-Et	76-77.5	33[c]	$C_{15}H_{14}O_2S$	C, H, S	14	33
3a	2-[PhS(O)]$C_6H_4CO_2H$	B-1	E-W	167.5-169.5	57	$C_{13}H_{10}O_3S$[g]	C, H, S[g]	19	0
		B-2	EA	168-169	85				
3b	2-[PhS(O)]$C_6H_4CH_2CO_2H$	B-2	E-W, EA	143-144[i]	74	$C_{14}H_{12}O_3S$	C, H, S	30	23
3c	2-[3'-F_3CPhS(O)]$C_6H_4CO_2H$	B-2	EA	193-194	67	$C_{14}H_9F_3O_3S$	C, H, F, S	4	2
3d	2-[2',3'-$(CH_3)_2$PhS(O)]$C_6H_4CO_2H$	B-2	M-W	206-208	77	$C_{15}H_{14}O_3S$	C, H, S, O	15	0
3e	2-[PhS(O)]$C_6H_4CH(CH_3)CO_2H$	B-2	E-W	166-169	80	$C_{15}H_{14}O_3S$	C, H, S	8	7
4a	2-[PhS(O_2)]$C_6H_4CO_2H$	C	B-H	144.5-145	71	*g*	*g*	15	0
4c	2-[3'-F_3CPhS(O_2)]$C_6H_4CO_2H$	C	B-H	146-148	70	$C_{14}H_9F_3O_4S$	H, F, S; C[j]	6	23
4d	2-[2',3'-$(CH_3)_2$PhS(O_2)]$C_6H_4CO_2H$	C	E-W	176-177	84	$C_{15}H_{14}O_4S$	C, H, S	0	27
Aspirin								<20[k]	~50[k]
Phenylbutazone								~50[k]	~50[k,l]

[a] These procedures followed the typical ones (A-C) of the Experimental Section, with various reagents being apportioned in the molar ratios of the amounts of starting materials. Procedures for 2b and 2e were multistep (see Experimental Section). [b] B, benzene; D, dioxane; E, ethanol; EA, ethyl acetate; Et, ethyl ether; H, hexane; M, methanol; W, water. A hyphen indicates use of a mixture. [c] Most syntheses involved only one step. For 2b, the yield is overall from 2a; for 2e, it is overall from 7. [d] Where analyses are indicated by symbols of the elements, except where otherwise noted, analytical results were within ±0.4% of the theoretical values. Ir spectra, and NMR spectra which were determined with ~50% of the compounds, were consistent with expectation. [e] At a dose of 50 mg/kg po × 2 (except for 35 mg/kg with 4c). [f] At a dose of 50 mg/kg po × 1. [g] Known compound. Melting point in reasonable agreement with reported values. See Experimental Section. Also, for 2b, J. O. Jilek et al. reported mp 123° [*Monatsh. Chem.*, 96, 182 (1965)], and Stoss and Satzinger reported mp 120° [*Chem. Ber.*, 105, 2575 (1972)]; for 2c, C. K. Pelz et al. reported mp 147.5-148.5° [*Collect. Czech. Chem. Commun.*, 34, 3936 (1969)]. [h] At 25 mg/kg, 0%. [i] For ^{18}O-labeled 3b, Numata et al. reported mp 247° dec but gave no analysis [*Int. J. Sulfur Chem., Part A*, 1, 1 (1971)]. [j] C: calcd, 50.92; found, 50.32. [k] See text for details. [l] At ~5 mg/kg rather than the usual 50 mg/kg.

reaction of the dipotassium salt of thiosalicylic acid with iodobenzene and cuprous oxide catalysis according to the method of Bacon and Hill, which they found effective for coupling other aryl halides with arenethiols.[11] The coupling was not catalyzed by copper metal, cuprous chloride, or cupric oxide; when these catalysts were used the predominant product was 2,2'-dithiodibenzoic acid, the corresponding disulfide. Coupling proceeded smoothly to give **2a** in high yield when cuprous oxide was used as a catalyst (in considerably less than reported[11] amounts). The latter method was adopted for the synthesis of **2c** and **2d** from appropriate aryl iodides. Where an unusual arenethiol may be available, a third method studied should be useful, that of coupling 2-iodobenzoic acid with the arenethiol using cuprous oxide as a catalyst. As in the previous instance, the coupling of 2-iodobenzoic acid with benzenethiolate ion was not catalyzed by copper metal (nor was that of the ester), cuprous chloride, or cupric oxide; virtually all of the iodobenzoic acid was recovered unchanged.

The homologated acid **2b** was prepared by the Arndt–Eistert synthesis from **2a** (eq 1). Best results were ob-

$$\mathbf{2a} \xrightarrow{SOCl_2} \underset{\mathbf{5}}{\text{2-(PhS)C}_6\text{H}_4\text{COCl}} \xrightarrow[Et_3N]{CH_2N_2} \underset{\mathbf{6}}{\text{2-(PhS)C}_6\text{H}_4\text{COCHN}_2} \xrightarrow[MeOH]{Ag_2O} \underset{\mathbf{7}}{[\text{2-(PhS)C}_6\text{H}_4\text{CH}_2\text{CO}_2\text{Me}]} \xrightarrow[2.\ H_3O^+,\ \Delta]{1.\ KOH,\ H_2O} \mathbf{2b} \qquad (1)$$

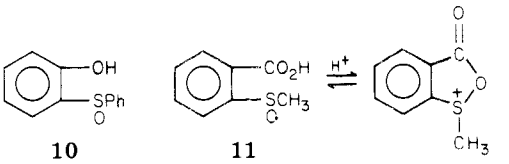
tained when the acid chloride **5** was allowed to react with a dried solution of diazomethane in the presence of triethylamine to scavenge hydrogen chloride. The subsequent Wolff rearrangement of the intermediate diazo ketone **6** was best accomplished in methanol, followed by basic hydrolysis of the unisolated ester **7** to yield the free acid **2b**. Direct rearrangement in aqueous media gave poor yields of the acid **2b**.

The α-methylated acid **2e** was prepared as eq 2 shows by carbethoxylation of the methyl ester **7**, followed by methylation using sodium ethoxide and methyl iodide, basic hydrolysis, and acid-catalyzed decarboxylation (without isolation of **8** or **9**, which probably were mixed methyl and ethyl esters).

$$\mathbf{7} \xrightarrow[NaOEt]{OC(OEt)_2} \underset{\mathbf{8}}{[\text{2-(PhS)C}_6\text{H}_4\text{CH(CO}_2\text{Et)}_2]} \xrightarrow[MeI]{NaOEt} \underset{\mathbf{9}}{[\text{2-(PhS)C}_6\text{H}_4\text{C(CH}_3)(\text{CO}_2\text{Et)}_2]} \xrightarrow[2.\ H_3O^+,\ \Delta]{1.\ OH^-} \mathbf{2e} \qquad (2)$$

The sulfoxides **3** were prepared by oxidation of the sulfides with either sodium metaperiodate[12] or *N*-chlorosuccinimide.[13] The oxidations with *N*-chlorosuccinimide were more satisfactory, since yields were somewhat higher than with metaperiodate. The sulfones **4** were obtained from the sulfides **2** using hydrogen peroxide in boiling acetic acid.[14]

Several of the sulfoxides show what appear to be interesting hydrogen-bonding effects, which seem most likely to be intramolecular. These warrant comment both because of their inherent interest and their possible relevance to receptor-site interactions. They are reflected in variations of the solid-state sulfoxide frequency (and in some degree of sharpening of the SO band) in the infrared as one goes from the acid to the ester. Thus the 2-carboxyphenyl phenyl sulfoxide **3a** shows ν_{SO} 975 cm^{-1}, which shifts to 1025 cm^{-1} upon methylation. The 3'-trifluoromethyl analogue **3c** showed a shift from 980 cm^{-1} for **3c** to 1035 cm^{-1} for its ester, and the 2',3'-dimethyl analogue from 960 cm^{-1} for **3d** to 1020 cm^{-1} for its ester. The probability that changes in hydrogen bonding are responsible for these shifts of ν_{SO}, and that the bonding is intramolecular rather than intermolecular, is suggested (cf. also ref 5a) by the assignment for **10** of ν_{SO} 994 cm^{-1} for the H-bonded form and 1034 cm^{-1} for the unassociated –S(O)– group.[15] Further evidence for interaction of S(O) and CO_2H is afforded in the finding by Allenmark and Hagberg of an anchimeric effect of CO_2H on racemization of an enantiomer of the methyl sulfoxide **11** that was reflected in the invoking of the intermediate **12**.[16] We found that the methyl sulfoxide **11** showed the same



10 **11** **12**

variation as the aryl counterparts in ν_{SO} from the acid **11** (ν_{SO} 950 cm^{-1}) to its ester (ν_{SO} 1030 cm^{-1}). The homologue (**3b**) of **3a** also shows the same kind of shift (ν_{SO} 987 cm^{-1} for **3b**, shifting to 1022 cm^{-1} after methylation).

Biological Results. Table I shows antiinflammatory activities of compounds **2**, **3**, and **4** in two conventional assays, for each of which 20% inhibition differs significantly from controls. In the carrageenan foot-edema assay,[17a] at doses of 50 mg/kg po × 2, aspirin effected essentially no inhibition and phenylbutazone ~50% (Table I). Two doses were used, since pharmacodynamics were unknown, to detect both compounds with relatively short onset of action and compounds with relatively long onset. Thus, with five male or female Holtzmann rats (180–190 g) in each group, doses were administered at 2.5 and 0.5 h prior to carrageenan injection. In the uv-erythema blocking assay,[17b] at doses of 50 mg/kg po × 1, aspirin effected ~50% inhibition; the ED_{50} of phenylbutazone was ~5 mg/kg. In the carrageenan assay, the two best compounds thus were better than aspirin but somewhat less active than phenylbutazone, i.e., 2-(phenylthio)benzoic acid (**2a**) and 2-(phenylsulfinyl)phenylacetic acid (**3b**). In the erythema assay, the two best compounds were roughly comparable to aspirin but were 2-(phenylthio)phenylacetic acid (**2b**) and 2-(*m*-trifluoromethylphenylthio)benzoic acid (**2c**). The randomness of these relationships to structure precludes drawing any general structure–activity conclusions. However, the view that sulfoxides might be useful counterparts of well-known antiinflammatory amines does seem to be vitiated by relative lack of promise of the sulfoxides **3a–e** and by the fact that each is less active than its sulfide (except for **3b** and **3d** in the edema assay). The two most interesting compounds in the edema and erythema assays, **2b** and its sulfoxide **3b**, had no significant activity in the in vivo adjuvant assay;[18] oral doses of 25 mg/kg per day were used, beginning 2 days prior to administration of adjuvant and extending for 18 days after this administration (total, 20 days). Approximate toxicities for ip doses warrant mention, as rough guides, although they show merely whether three mice (or, rarely, two) survived the lower dose but died at the higher; in g/kg, these were 0.1–0.3 for **2c**, 0.3–1.0 for **2a,b,d,e**, **3a,c**, **4a,c,d**, and >1.0 for **3b**; amounts available of **3d** and **3e** were too small for tests.

Experimental Section

Melting points, determined in a Thomas-Hoover stirred-liquid apparatus, are corrected. Elemental analyses were by Galbraith Laboratories Inc., Knoxville, Tenn. Ir spectra were done in KBr pellets, unless otherwise specified, using either a Beckman Model IR-10 or Perkin-Elmer Model 727 spectrophotometer. NMR spectra were recorded with a Joelco JNM-MH-100 NMR spec-

trometer with Me_4Si as an internal standard. All removals of solvent and concentrations specified were done under reduced pressure with a rotating-flask evaporator. Where analyses are indicated by symbols of the elements, analytical results for these elements were within ±0.4% of the theoretical values.

Materials. 3-Iodobenzotrifluoride and 2,3-dimethyliodobenzene, used in the preparation of sulfides **2c** and **2d**, were obtained conventionally by diazotizing the commercially available amines (Aldrich), treating with potassium iodide, and distilling the product under reduced pressure. The methyl 2-carboxyphenyl sulfoxide 11 (mp and lit.[19] mp 176–178°) was prepared by methylation of thiosalicylic acid with dimethyl sulfate,[20] followed by oxidation of the sulfide (mp and lit.[20] mp 168–169°) with $NaIO_4$. The 2-carboxyphenyl sulfoxides were methylated for the ir studies by allowing an Et_2O solution of the acid to react with a slight excess of CH_2N_2 in Et_2O, evaporating the Et_2O, and taking the ir spectra of the crystalline residues in KBr pellets.

Preparation of Sulfides. 2-(Phenylthio)benzoic Acid (2a). Procedure A-1. From Anthranilic Acid. In a procedure modified from one of Weedon,[10] anthranilic acid (41.0 g, 300 mmol) was dissolved by gentle warming in 200 ml of H_2O and 64 ml of concentrated HCl. The solution was cooled to 0° (the salt precipitated) and diazotized (0–5°) with a solution of 22 g (319 mmol) of $NaNO_2$ in 45 ml of H_2O. The diazonium salt solution was stirred at 0° for 30 min and then was kept at 0° while it was added dropwise at 0° during 2.5 h to a rapidly stirred solution of thiophenol (34.0 g, 309 mmol) in 300 ml of H_2O containing 60 g (1500 mmol) of NaOH and 3 g of copper powder (Fisher). Since addition was done at lower than the usual temperature,[10] we took care that N_2 evolution proceeded smoothly during the addition, so that the presumably explosive diazo sulfide did not accumulate. The mixture then was stirred at 0° for 1 h and allowed to warm to ~25° overnight. It then was heated on a steam bath for 1 h and cooled. Solid was removed by filtration and washed with 200 ml of cold H_2O. The combined filtrates were acidified with concentrated HCl. The brown precipitate was collected and recrystallized successively from a minimum of EtOH, EtOH–H_2O (3:2), and benzene–hexane (twice). The yield was 42.0 g (61%) of tan **2a**, mp 168–171° (lit.[10] 166°).

Procedure A-2. From 2-Iodobenzoic Acid. A 1-l. flask fitted with a Dean-Stark trap and condenser, stirrer, and an addition funnel was charged with 2-iodobenzoic acid (62.0 g, 250 mmol), thiophenol (27.5 g, 250 mmol), and 200 ml of benzene. A solution of KOH (66 g, 1000 mmol assuming the KOH to be 85% pure) in 100 ml of H_2O was added. The mixture was heated to reflux, and H_2O was collected until no more appeared (~5 h, ~115 ml). Nearly all of the benzene then was removed by distillation at atmospheric pressure and was replaced with 500 ml of DMF. The solution was heated until the distillation temperature reached 150° and then was cooled to about 100°. Cuprous oxide (3.0 g, 21 mmol, Fisher C-477) was added, and the mixture was brought *carefully* to gentle reflux (care must be taken since the reaction became quite vigorous near the reflux temperature). The mixture was heated at reflux with vigorous stirring for 12 h. The brown solution then was cooled to room temperature and poured onto 1000 g of ice. The basic mixture was filtered and acidified with concentrated HCl. The white precipitate was collected and recrystallized from EtOH–H_2O (3:2). The yield was 47.0 g (82%) of white crystalline **2a**, mp 169–171°, undepressed by **2a** prepared according to A-1.

Procedure A-3. From Thiosalicylic Acid. A 1-l. flask fitted as in A-2 was charged with KOH (68 g, ~1 mol assuming 85% KOH) in 70 ml of H_2O. Thiosalicylic acid (77.0 g, 500 mmol) was added with 300 ml of benzene. As in A-2, H_2O (~95 ml) was removed by azeotropic distillation, and nearly all of the benzene then was removed by distillation. DMF (500 ml) was added, and the mixture was heated until the distillation temperature reached 150°. An additional 100 ml of DMF along with 2.5 g (17.5 mmol) of Cu_2O (Fisher C-477) was added. The rapidly stirred mixture was brought to gentle reflux and iodobenzene (104 g, 510 mmol) was added dropwise over 45 min. Reflux was continued for 16 h. The slushy mass was cooled and mixed with 1.8 l. of ice water, 10 g of KOH was added (to redissolve some acid that precipitated), and the mixture was filtered. The filtrate was extracted with two 150-ml portions of $CHCl_3$ and the extracts were discarded. The aqueous phase was acidified with concentrated HCl and the precipitated **2a** was collected and recrystallized from EtOH–H_2O (3:2). The yield of **2a** after drying under vacuum at 60° for 12 h was 101 g as white needles (88%), mp 168.5–171°, undepressed by the **2a** prepared in A-1 and A-2.

Preparation of Sulfoxides. 2-(Phenylsulfinyl)benzoic Acid (3a). Procedure B-1. Oxidation with Sodium Metaperiodate. A solution of 2-(phenylthio)benzoic acid (**2a**, 11.5 g, 50.0 mmol) in 100 ml of MeOH was chilled to 0° and poured into 100 ml of aqueous 0.51 M sodium metaperiodate at 0°. The mixture was stirred overnight at 0°, and the solvents were removed. The solid residue was washed with H_2O and recrystallized from EtOH–H_2O. The yield was 7.0 g (57%) of white **3a**, mp 167.5–169.5° (lit.[10] 163°). The mixture melting point with the sulfide **2a** was considerably depressed: ir 3200–2100, 1685, 1440, 1240, 975 cm^{-1} (SO). Anal. ($C_{13}H_{10}O_3S$) C, H, S.

Procedure B-2. Oxidation with *N*-Chlorosuccinimide. 2-(Phenylthio)benzoic acid (**2a**, 23.0 g, 100 mmol) was dissolved in 50 ml of MeOH. *N*-Chlorosuccinimide (13.3 g, 100 mmol) was added in one portion, and the mixture was stirred at 0° for 2 h and then at ~25° overnight. The solvent was removed, and the residue was stirred well in H_2O while being extracted with Et_2O. The extract was dried ($MgSO_4$) and evaporated, and the residue was suspended in 100 ml of 10% aqueous KOH. This mixture was heated on a steam bath for 2 h (to saponify any methyl ester), cooled, and extracted with 50 ml of Et_2O. The aqueous layer was acidified with 6 N HCl. The precipitate was extracted four times with 50-ml portions of Et_2O. The extract was dried ($MgSO_4$), filtered, and concentrated. The oily residue hardened and was recrystallized from EtOAc. The yield was 21.0 g (85%) of white crystalline **3a**, mp 168–169°, undepressed by **3a** prepared according to procedure B-1.

Procedure C. Preparation of Sulfones. 2-(Phenylsulfonyl)benzoic Acid (4a). 2-(Phenylthio)benzoic acid (6.9 g, 30 mmol) was dissolved in 100 ml of AcOH, and H_2O_2 (20.4 g of 30% solution) was added. The solution was heated under reflux for 20 h. The mixture was cooled and diluted with 500 ml of H_2O and extracted with five 75-ml portions of CH_2Cl_2. The combined extracts were washed with H_2O, dried ($MgSO_4$), filtered, and concentrated. The residue solidified and was recrystallized from benzene–hexane. The yield of white crystalline **4a** was 5.6 g (71%), mp 144.5–145° (lit.[10] 143°).

2-(Phenylthio)phenylacetic Acid (2b). A. 2-(Phenylthio)benzoyl Chloride (5). A suspension of 23.0 g (100 mmol) of **2a** in 25 ml of benzene was stirred magnetically at ~25° while 15 ml of $SOCl_2$ (~200 mmol, purified by distillation from boiled linseed oil, then from quinoline) in 15 ml of benzene was added during 45 min. After the rapid evolution of gas ceased, the mixture was heated under reflux for 2 h. The clear solution was cooled, and all volatile materials were evaporated at 50°. The residual oil was taken up in 25 ml of Et_2O, and 50 ml of hexane was added. Crystals formed immediately. The mixture was cooled, and the greenish yellow solid was separated by filtration. The product was recrystallized from hexane–Et_2O using decolorizing carbon. The yield of yellow crystalline **5** was 22.0 g (89%), mp 67–69°. Anal. ($C_{13}H_9ClOS$) C, H, Cl, S.

B. ω-Diazo(2-phenylthio)acetophenone (6). Alcohol-free CH_2N_2 (~70 mmol) was prepared by distillation from a mixture of aqueous KOH–diethylene glycol monomethyl ether–Et_2O with slow addition of a solution of *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide (Diazald, Aldrich) in Et_2O. The Et_2O solution of CH_2N_2 (about 250 ml) was dried at 0° over 5 g of KOH for 3 h and then was carefully decanted into a 500-ml flask with polished joints that was fitted with a drying tube and addition funnel. Triethylamine (7.0 g, 69 mmol, dried over KOH) was added, and the solution was stirred for a few minutes at 0°. The chloride **5** (15.1 g, 61 mmol) in 75 ml of Et_2O then was added during 30 min with magnetic stirring. After the addition was about one-third complete, a white precipitate began to appear. The mixture was stirred for 2 h more at 0° and then was stored at 0° overnight. The $Et_3N{\cdot}HCl$ was separated by filtration through a fluted paper, and Et_2O was removed from the filtrate at 0°. The residual brown oil was dissolved in 50 ml of benzene, 50 ml of hexane was added, and the solution was set aside at 0° for 36 h. The yellow needles that formed amounted to 11.2 g of **6**, mp 53–55°. Concentration of the mother liquor gave 2.2 g more of **6**: mp 53–55°; total yield of **6**, 13.4 g (86%); ir (neat melt) 2100, 1600, 1460, 1430, 1355 cm^{-1};

NMR ($CDCl_3$) δ 5.78 (s, 1 H), 6.9–7.6 (m, 9 H). Anal. ($C_{14}H_{10}N_2OS$) C, H, N, S.

C. 2-(Phenylthio)phenylacetic Acid (2b). The diazo ketone **6** (11.4 g, 45.0 mmol) was dissolved in 50 ml of absolute MeOH in a flask protected by a drying tube. The magnetically stirred solution was heated in a water bath at 55–60° and 200 mg of Ag_2O (Fisher) was added. After a few minutes, gas evolution began and continued for about 30 min. A second portion of Ag_2O then was added, and the mixture was heated for 30 min more, cooled, and allowed to stand overnight. The catalyst was removed by filtration through a Celite mat, and the solvent was evaporated to give the brown oily methyl ester **7**.

The crude **7** was purified by chromatography on alumina (Woelm, dry column) by elution with hexane–ether: ir (neat) 1740, 1585, 1470, 1430, 1330, 1250, 1220, 1160 cm^{-1}. No further purification was attempted because **7** decomposed when distillation under high vacuum was attempted.

Since the purification of **7** proved to be difficult, the crude **7** obtained in a reaction identical with the above was dissolved in 50 ml of MeOH and 50 ml of 10% aqueous KOH. The mixture was heated at reflux for 2 h, cooled, and evaporated to dryness. The residue was dissolved in 100 ml of H_2O, and the solution was extracted with two 50-ml portions of Et_2O. The aqueous layer then was acidified with 6 N HCl. Precipitate was collected and recrystallized twice each from EtOH–H_2O and EtOAc. The yield was 8.8 g (80%) of white crystalline **2b**: mp 121–122°; ir 3200–2400, 1700, 1400, 1230 cm^{-1}; NMR (CCl_4) δ 3.82 (s, 2 H), 7.07 (broad s, 9 H), 10.12 (broad, 1 H). Anal. ($C_{14}H_{12}O_2S$) C, H, S.

2-(2'-Phenylthio)phenylpropionic Acid (2e). A solution of NaOEt was prepared by adding 1.20 g (0.052 g-atom) of clean Na metal to 30 ml of absolute EtOH in a flask with a reflux condenser and drying tube. A solution of 12.9 g (50.0 mmol) of the methyl ester **7**, prepared and chromatographed as described above, in 10 ml of absolute EtOH was added through the condenser, followed by 40 ml of $CO(OEt)_2$. The condenser was set downward for distillation, and the mixture was distilled slowly (~2 h) until the distillation temperature reached 125°. The cooled semisolid residue was thoroughly mixed with 50 ml of cold H_2O, and the mixture was extracted with five 50-ml portions of Et_2O. The Et_2O solution was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residual oil (16 g) was chromatographed on 185 g of alumina (Woelm I, neutral). Elution with 200 ml of petroleum ether gave a small amount of unidentified oily forerun; then elution with 200 ml of petroleum ether–ether 9:1 gave 13.5 g of yellow oil. Continued elution gave no further product. The oily product (78% yield, assuming no methyl ester component) was identified as the monosubstituted malonic ester **8** by ir and NMR; it was used without further purification.

A solution of NaOEt was prepared by dissolving 0.575 g (0.025 g-atom) of carefully cleaned Na metal in 20 ml of absolute EtOH (freshly distilled from NaOEt–diethyl phthalate) in a flask fitted with an addition funnel, reflux condenser with drying tube, and thermometer. The solution was cooled to 0°, and a solution of the malonate **8** (8.60 g, 25.0 mmol, assuming absence of methyl ester) in 10 ml of absolute EtOH was added. The mixture was stirred at 0° for 20 min, and 3.55 g (25.0 mmol) of MeI in 10 ml of absolute EtOH was then added. Stirring at 0° was continued for 1 h. The mixture then was heated at reflux until it was neutral to moist litmus (~1 h). Solvent was removed, the residue was taken up in 50 ml of Et_2O, and the Et_2O solution was washed with H_2O, 5% aqueous $NaHCO_3$, and again with H_2O. The Et_2O layer was dried ($MgSO_4$) and concentrated. The residual oil was heated at reflux overnight with 100 ml of 10% KOH in 1:1 H_2O–EtOH. The mixture was cooled at 80°, and concentrated HCl was added dropwise. After the mixture became acidic, foaming occurred with each additional drop of HCl. A total of 25 ml of concentrated HCl was added. Decarboxylation was completed by heating at reflux for 1 h. The mixture was cooled and extracted with five 50-ml portions of Et_2O. The combined extracts were washed with H_2O, dried ($MgSO_4$), and concentrated. The resulting oil crystallized when rubbed with petroleum ether at dry ice temperature. The yield was 5.1 g of light yellow **2e**, mp 62–78°. After recrystallization from petroleum ether–Et_2O, 3.0 g of **2e** resulted, mp 73–77°, which was chromatographed on 200 g of alumina (Woelm, V, acid-washed). Elution with 400 ml of hexane gave 0.1 g of by-product and hexane–ether (2:3) then gave 2.7 g (33% overall from **7**) of white **2e**: mp 76–77.5°; ir 3100–2400, 1700, 1580 (w), 1470 (w), 1438 (w), 1375 (w), 1320, 1300, 1225 cm^{-1}; NMR (CCl_4) δ 12.12 (s, 1 H), 7.05–7.44 (complex multiplet, 9 H), 4.43 (quartet, 1 H), 1.19 (doublet, 3 H). Anal. ($C_{15}H_{14}O_2S$) C, H, S.

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