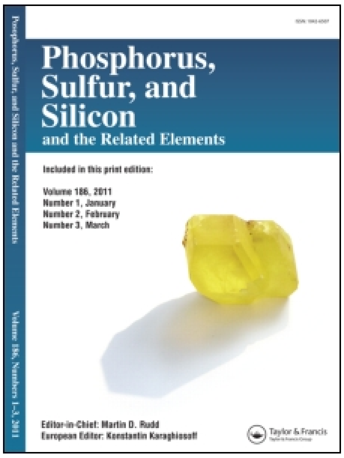

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SYNTHESIS AND SPECTRAL STUDIES OF ALKYL-3- [(SUBSTITUTED PHENYLTHIO)METHYL] BENZOATES AND THEIR PHENYL SULFONYL DERIVATIVES

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SYNTHESIS AND SPECTRAL STUDIES OF ALKYL-3-[(SUBSTITUTED PHENYLTHIO)METHYL] BENZOATES AND THEIR PHENYL SULFONYL DERIVATIVES

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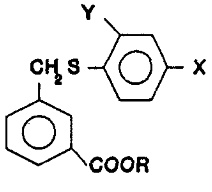
New methyl and ethyl-3-[(substituted phenylthio)methyl] benzoates and their corresponding phenyl sulfonyl derivatives have been synthesized and identified by UV, IR and ^{1}HNMR. Both phenylthio 1 and 2 as well as phenyl sulfonyl derivatives 3 and 4 showed a linear relationship between chemical shift δ ppm of the benzylic protons and σ-Hammett constants.

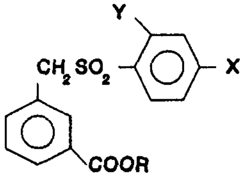
Key words: Arylthio; aryl sulfonyl benzoates; ^{1}HNMR.

During our studies directed towards the synthesis of novel benzyl aryl sulfides, sulfoxides and sulfones[1–6] of potential herbicidal[7] and insecticidal[8] activities, we noticed with interest several reports on analogous compounds which exhibit unique chemotherapeutic and herbicidal activities.[9]

Our arylthio and aryl sulfonyl benzoic acid derivatives showed a toxicity towards the Mosquito larvae of culex pipiens molestus Forskal and Aedes caspius pallas.[8] It was found that the introduction of nitro group has a powerful toxiphoric effect and the biological activity is increased in presence of —OCH$_3$, —COOH or Br substituents. Also, it was reported that the sulfones are more toxic than their corresponding sulfides.[8] Some of these compounds were found to be effective against bacteria as well as being nontoxic to the tested crops, including weeds.[7] Thus, we report here the synthesis of a new series of methyl and ethyl-3-[(substituted phenylthio)methyl] benzoates **1a–g** and **2a–g**, respectively, and their corresponding phenyl sulfonyl derivatives **3a–e,g** and **4a–e,g** to evaluate their activities.



1a-g, 2a-g



3a-e,g , 4a-e,g

1,3, R=CH$_3$; a,x=Y=H; b,x=CH$_3$,Y=H; c,X=OCH$_3$,Y=H; d,x=Br,Y=H;
e,x=Cl,Y=H; f,x=H,Y=COOH; g,x=H,Y=-COOCH$_3$
2,4,R=C$_2$H$_5$; a,x=Y=H; b,x=CH$_3$,Y=H; c,X=OCH$_3$,Y=H; d,x=Br,Y=H;
e,x=Cl,Y=H; f,x=H,Y=COOH; g,x=H,Y= -COOC$_2$H$_5$

TABLE I

Properties, analysis, UV and ^{1}H NMR spectra of methyl and ethyl-3-[(arylthio)methyl] benzoates **1a–g** and **2a–g**, respectively

Cpd.	Yield %	m.p. °C n^{20}_D	λmax^{i}, nm (ϵ)x10^{-4}	^{1}HNMR (δ ppm, acetone - d_6)								Molecular formula	%calcd (% found)
				CH_3 ester	CH_2 ester	CH_2 benzylic	C_2	$C_{4,6}$	C_5	$C_{2',6'}$	$C_{3',5'}$		
1a	78	1.5930	213 (2.03)	3.75 (s,3H)		4.10 (s,2H)	7.85 (s,1H)	7.35 (d,2H)	7.35 (t,1H)	7.15 (s,2H)	7.15 (s,3H);($C_{4'}$)	$C_{15}H_{14}SO_2$	C,69.76;H,5.42;S,12.40 (C,69.60;H,5.60;S,12.60)
b^{ii}	82	1.5870	2.09 (2.14)	3.75 (s,3H)		4.05 (s,2H)	7.85 (s,1H)	7.75 (d,2H)	7.29 (t,1H)	6.90 (d,2H)	7.10 (d,2H)	$C_{16}H_{16}SO_2$	C,70.58;H,5.88;S,11.76 (C,70.10;H,5.80;S,11.40)
c^{iii}	72	1.5889	2.07 ((0.12)	3.72 (s,3H)		4.00 (s,2H)	7.75 (s,1H)	7.68 (d,2H)	7.05 (t,1H)	6.65 (d,2H)	7.20 (d,2H)	$C_{16}H_{16}SO_3$	C,66.66;H,5.55;S,11.11 (C,66.20;H,5.50;S,11.00)
d	87	31	2.10 (1.80)	3.75 (s,3H)		4.15 (s,2H)	7.85 (s,1H)	7.75 (d,2H)	7.40 (t,1H)	7.20 (d,2H)	7.35 (d,2H)	$C_{15}H_{13}BrSO_2$	C,53.41;H,3.85;S,9.49 (C,53.10;H,3.60;S,9.40)
e	81	1.5803	2.26 (1.90)	3.80 (s,3H)		4.05 (s,2H)	7.50 (s,1H)	7.80 (d,2H)	7.35 (t,1H)	7.15 (s,2H)	7.15 (s,2H)	$C_{15}H_{13}ClSO_2$	C,61.64;H,4.45;S,10.59 (C,61.70;H,4.10;S,10.80)
										$C_{3'}$ $C_{6'}$	$C_{4',5'}$		
f	88	158	2.10 (2.49)	3.80 (s,3H)		4.30 (s,2H)	8.05 (s,1H)	8.00 (d,2H)	7.65 (t,1H)	7.89 7.45 (d,1H) (d,1H)	7.25 (t,1H)	$C_{16}H_{14}SO_4$	C,63.57;H,4.63;S,10.59 (C,63.40;H,4.20;S,10.30)
g	92	54	2.23 (1.61)	3.80 (s,6H)		4.28 (s,2H)	8.00 (s,1H)	7.85 (d,2H)	7.70 (t,1H)	7.80 7.45 (d,1H) (d,1H)	7.20 (t,2H)	$C_{17}H_{16}SO_4$	C,64.55;H,5.06;S,10.12 (C,64.30;H,5.50;S,10.2)
2a	69	1.5770	2.09 (0.25)	1.35 (t,3H)	4.30 (q,2H)	4.00 (s,2H)	7.90 (s,1H)	7.80 (d,2H)	7.25 (t,1H)	7.15 (s,2H)	7.15 (s,3H;$C_{4'}$)	$C_{16}H_{16}SO_2$	C,70.58;H,5.88;S,11.76 (C,71.00;H,5.40;S,11.90)
b^{iv}	78	1.5740	2.26 (1.53)	1.32 (t,3H)	4.28 (q,2H)	3.95 (s,2H)	7.84 (s,1H)	7.80 (d,2H)	7.18 (t,1H)	7.00 (d,2H)	7.30 (d,2H)	$C_{17}H_{18}SO_2$	C,71.32;H,6.29;S,11.18 (C,71.60;H,6.70;S,11.50
c^{v}	71	1.5860	2.30 (1.70)	1.30 (t,3H)	4.25 (q,2H)	3.85 (s,2H)	7.82 (s,1H)	7.78 (d,2H)	7.15 (t,1H)	6.95 (d,2H)	7.12 (d,2H)	$C_{17}H_{18}SO_3$	C,67.54;H,5.96;S,10.59 (C,67.40;H,5.80;S,10.60)
d	86	1.5782	2.28 (3.95)	1.30 (t,3H)	4.25 (q,2H)	4.15 (s,2H)	7.85 (s,1H)	7.75 (d,2H)	7.20 (t,1H)	7.00 (d.2H)	7.30 (d,2H)	$C_{16}H_{15}BrSO_2$	C,54.76;H,4.27;S,9.11 (C,55.20;H,4.50;S,9.00)
e	83	1.5878	2.26 (1.66)	1.35 (t,3H)	4.30 (q,2H)	4.12 (s,2H)	7.85 (s,1H)	7.75 (d,2H)	7.20 (t,1H)	7.05 (d,2H)	7.05 (d,2H)	$C_{16}H_{15}ClSO_2$	C,62.74;H,4.90;S,10.54 (C,62.50;H,5.30;S,10.80)
										$C_{3'}$ $C_{6'}$	$C_{4',5'}$		
f	91	192	2.10 (2.30)	1.35 (t,3H)	4.28 (q,2H)	4.25 (s,2H)	8.05 (s,1H)	7.98 (d,2H)	7.65 (t,1H)	7.90 7.49 (d,1H) (d,1H)	7.40 (t,2H)	$C_{17}H_{16}SO_4$	C,64.55;H,5.06;S,10.12 (C,64.30;H,4.90;S,10.50)
g	88	42	2.23 (1.64)	1.30 (t,3H)	4.30 (q.2H)	4.22 (s,2H)	8.05 (s,1H)	7.90 (d,2H)	7.65 (t,1H)	7.85 7.45 (d,1H) (d,1H)	7.40 (t,2H)	$C_{19}H_{20}SO_4$	C,66.27;H,5.81;S,9.30 (C,65.90;H,5.90;S,9.39)

i) In ethanol, ii) 4'-CH_3 appeared at δ 2.15 ppm (s, 3H), iii) 4'-OCH_3 appeared at δ 3.55 ppm (s, 3H), iv) 4'-CH_3 appeared at δ 2.20 ppm (s, 3H), v) 4'-OCH_3 appeared at δ 3.62 ppm (s, 3H).

TABLE II

Properties, analysis, UV and ^{1}H NMR spectra of methyl and ethyl-3-[(aryl sulfonyl)methyl] benzoates **3a–g** and **4a–g** respectively

Cpd.	Yield %	m.p.°C	λ_{max}^{i},nm (ϵ)x10^{-4}	†H NMR (δ ppm., acetone - d_6)								Molecular formula	%calcd (% found)
				CH_3 ester	CH_2 ester	CH_2 benzylic	C_2	$C_{4,6}$	C_5	$C_{2',6'}$	$C_{3',5'}$		
3a	92	71	218 (1.38)	3.78 (s,3H)		4.56 (s,2H)	7.78 (s,1H)	7.55 (d,2H)	7.80 (t,1H)	7.25 (s,2H)	7.25 (s,3H;$C_{4'}$)	$C_{15}H_{14}SO_4$	C,62.06;H,4.82;S,11.03 (C,62.40;H,4.50;S,11.20)
b^{ii}	94	78	226 (1.89)	3.82 (s,3H)		4.55 (s,2H)	7.75 (s,1H)	7.48 (d,2H)	7.85 (t,1H)	7.35 (d,2H)	7.25 (d,2H)	$C_{16}H_{16}SO_4$	C,63.15;H,5.26;S,9.50 (C,63.40;H,4.70;S,9.40)
c^{iii}	79	91	237 (1.51)	3.85 (s,3H)		4.50 (s,2H)	7.70 (s,1H)	7.50 (d,2H)	7.85 (t,1H)	7.30 (d,2H)	6.95 (d,2H)	$C_{16}H_{16}SO_5$	C,60.00;H,5.00;S,10.00 (C,59.60;H,4.70;S,9.90)
d	90	118	233 (2.65)	3.82 (s.3H)		4.65 (s,2H)	7.75 (s,1H)	7.60 (d,2H)	7.85 (t,1H)	7.28 (d,2H)	7.45 (d,2H)	$C_{15}H_{13}BrSO_4$	C,48.78;H,3.52;S,8.67 (C,48.60;H,3.90;S,8.50)
e	89	95	228 (2.32)	3.88 (s,3H)		4.62 (s,2H)	7.80 (s,1H)	7.60 (d,2H)	7.92 (t,1H)	7.35 (s,2H)	7.35 (s,2H)	$C_{15}H_{13}ClSO_4$	C,55.55;H,4.01;S,9.87 (C,55.10;H,3.90;S,9.50)
g	70	120	215 (1.90)	3.80 3.95 (2s,6H)		4.82 (s,2H)	7.88 (s,1H)	7.35 (d,2H)	7.65 (t,1H)	$C_{3'}$ 7.72 (d,1H) $C_{6'}$ 7.45 (d,1H)	$C_{4',5'}$ 7.25 (t,1H)	$C_{17}H_{16}SO_6$	C,58.62;H,4.59;S,9.19 (C,58.40;H,4.60;S,9.40)
4a	82	49	219 (1.94)	1.30 (t,3H)	4.28 (q,2H)	4.55 (s,2H)	7.75 (s,1H)	7.60 (d,2H)	7.90 (t,1H)	7.40 (s,2H)	7.40 (s.3H;$C_{4'}$)	$C_{16}H_{16}SO_4$	C,63.15;H,5.26;S,10.52 (C,63.40;H,5.50;S,9.90)
b^{iv}	84	52	226 (2.16)	1.35 (t,3H)	4.30 (q,2H)	4.50 (s,2H)	7.75 (s,1H)	7.55 (d,1H)	7.90 (t,1H)	7.35 (d,2H)	7.28 (d,2H)	$C_{17}H_{18}SO_4$	C,64.15;H,5.66;S,10.06 (C,64.20;H,5.60;S,10.20
c^{v}	87	81	239 (1.51)	1.30 (t,3H)	4.25 (q,2H)	4.45 (s,2H)	7.75 (s,1H)	7.56 (d,2H)	7.85 (t,1H)	7.35 (d,2H)	7.18 (d,2H)	$C_{17}H_{18}SO_5$	C,61.07;H,5.38;S,9.58 (C,61.00;H,5.40;S,9.60)
d	88	88	234 (2.91)	1.35 (t,3H)	4.30 (q,2H)	4.60 (s,2H)	7.60 (s,1H)	7.65 (d,2H)	7.80 (t,1H)	7.30 (d,2H)	7.40 (d,2H)	$C_{16}H_{15}BrSO_4$	C,53.26;H,3.91;S,8.35 (C,53.10;H,4.10;S,8.00)
e	91	104	227 (2.48)	1.28 (t,3H)	4.18 (q,2H)	4.57 (s,2H)	7.75 (s,1H)	7.45 (d,2H)	7.78 (t,1H)	7.30 (s,2H)	7.30 (s,2H)	$C_{16}H_{15}ClSO_4$	C,60.35;H,4.43;S,9.46 (C,60.60;H,4.80;S,9.70)
g	87	52	218 (2.70)	1.30 (t,3H)	4.25 (q,2H)	4.90 (s,2H)	7.82 (s,2H)	7.50 (d,2H)	7.90 (t,1H)	$C_{3'}$ 7.70 (d,1H) $C_{6'}$ 7.35 (d,1H)	$C_{4',5'}$ 7.32 (t,2H)	$C_{18}H_{20}SO_6$	C,57.44;H,5.31;S,8.51 (C,57.70;H,5.00;S,8.90)

i) In ethanol, ii) 4′-CH_3 appeared at δ 2.40 ppm (s, 3H), iii) 4′-OCH_3 appeared at δ 3.45 ppm (s, 3H), iv) 4′-CH_3 appeared at δ 2.45 ppm (s, 3H), v) 4′-OCH_3 appeared at δ 3.62 ppm (s, 3H)

†To whom correspondence should be addressed.

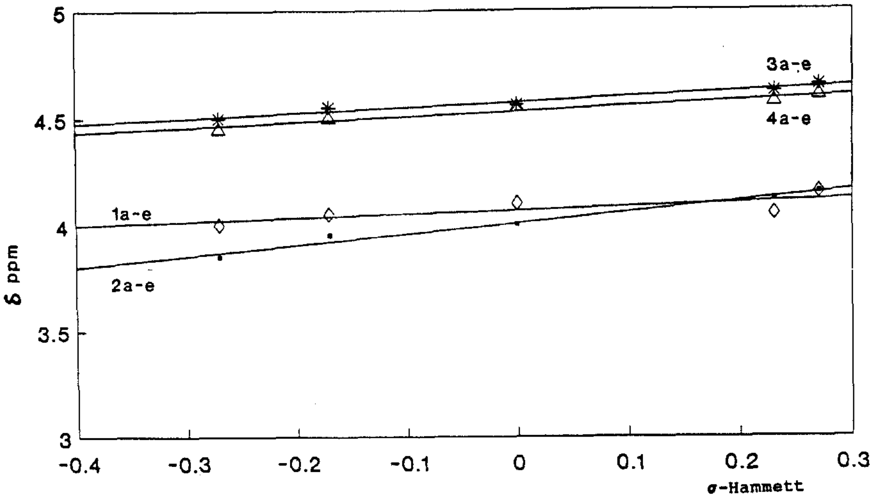


FIGURE 1 δ ppm values of the benzylic protons of the sulfides **1a–e**, **2a–e** and the sulfones **3a–e** and **4a–e** against σ-Hammett constants.

The sulfide esters **1a–g** and **2a–g** were prepared by the reaction of methyl or ethyl 3-chloromethyl benzoates[10] with substituted thiophenols in presence of sodium alkoxide. The sulfone esters **3a–e,g** and **4a–e,g** were obtained by treating of 3-[(substituted phenyl sulfonyl)methyl]benzoic acids[11] with methyl and ethyl alcohol respectively, in presence of catalytic amount of sulfuric acid.

The ^{1}HNMR δ chemical shifts of the benzylic protons for the sulfides **1a–e**, **2a–e** and the sulfones **3a–e**, **4a–e** correlate nicely with σ-Hammett constants (Figure 1). This is explained on the basis that 4′-substituent can resonate with the sulfur atom, in case of electron donating substituents e.g., OCH_3,[12] while electron withdrawing substituents e.g., NO_2 attract electrons from sulfur atom, leading to a change in the influence of thioaryl and aryl sulfonyl groups on the chemical shift of benzylic protons, i.e., the difference in the chemical shift is presumably due to the intrinsic effect of the relayed electrostatic force from full or partial charge imposed at the sulfur atom. This behaviour suggests that the thio ether linkage and the sulfonyl group can transmit the electrical effect of 4′-substituent.

The IR spectra of the studied compounds showed sharp bands at 1735–1750 cm^{-1} (C=O) beside a characteristic stretching band at 635–650 cm^{-1} due to (C—S) bond for the sulfides **1a–g**, **2a–g** and a strong absorption band at 1350 cm^{-1}, 1160 cm^{-1} for the asymmetric and symmetric (SO_2) stretching for the sulfones **3a–e,g**, **4a–e,g**. The physical properties, analysis, UV and ^{1}HNMR of the sulfides and sulfones are compiled in Tables I and II respectively.

EXPERIMENTAL

Melting points are uncorrected and were determined on a Thomas-Hoover capillary apparatus, refractive index values were measured on PZO, RLi AAB refractometer. ^{1}HNMR spectra were obtained in acetone-d_6 using bruker AM 300 L spectrometer and the IR spectra (KBr pellets or Nujol) were measured on a Pye Unicam Cambridge SP^3 200 instrument. UV spectra were measured on UV-Visible recording spectrophotometer 160-A Shimatzu. Analytical thin-layer chromatograph (tlc) was carried out on silica gel using (1:9) petroleum ether: ethyl acetate. Elemental analysis were carried out in the Faculty of Science, Cairo University, Egypt.

General procedure for the synthesis of sulfides **1a–g** and **2a–g**: Methyl or ethyl 3-chloromethyl benzoate[10] (0.1 mole) in absolute methanol or ethanol and the sodium salt of the thiol (0.1 mole) were refluxed for 1–2 hours. Cooling, dilution and acidification by aqueous acid gave either a solid, which was purified by recrystallization from aqueous ethanol, or a liquid which was extracted with ether and purified by column chromatography using 1:9 petroleum ether:ethylacetate as eluent. **1g** and **2g** were synthesized by 10 hours reflux of **1f** and **2f** in a mixture of absolute methyl or ethyl alcohol and catalytic amount of concentrated sulfuric acid. Cooling, diluting and washing with aqueous sodium bicarbonate gave solids which were recrystallized from aqueous ethanol.

General procedure for the synthesis of the sulfones **3a–e,g** and **4a–e,g**: Acid sulfones[11] were refluxed for 10 hours in a mixture of absolute methanol or ethanol and few drops of concentrated sulfuric acid. On cooling, dilution and washing with sodium bicarbonate solution, solids were obtained and recystallized from aqueous alcohol.

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