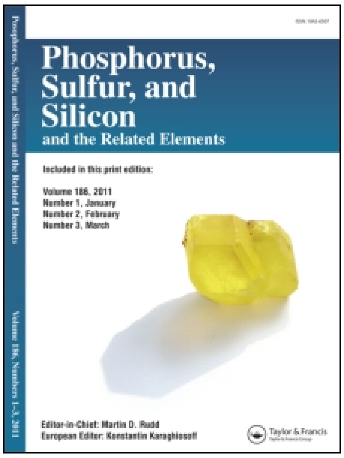

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SYNTHESIS, SPECTRAL STUDIES AND C-S, C-N BOND FISSIONS OF SOME NOVEL N-[ALKYL (4′- SUBSTITUTED PHENYLTHIO)] PHTHALIMIDES*

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N-[(4'-Substituted phenylthio)ethyl] phthalimide 1a-g and their corresponding n-propyl 2a-g, n-butyl 3a-g derivatives have been synthesised. The structure of these compounds were proved by UV, IR, ^1H NMR, ^{13}CMR and mass spectra. The ^1H and ^{13}C chemical shifts of the adjacent methylene protons and carbons of both the sulfur atom and phthalimido nitrogen group were reasonably correlated using σ° values. The carbon-nitrogen and the carbon-sulfur bond fissions in alkaline and acidic media were discussed.

Keywords: Arylthio alkyl phthalimides; ^1HNMR; ^{13}CMR; mass spectra; C-S and C-N bond fissions

INTRODUCTION

Previously we have described the synthesis of different series of diaryl, aryl benzyl, aryl picryl, aryl heterocyclic sulfides, sulfoxides and sulfones as well as aryl mercapto acetates and propionates[1–8]. The mechanisms of the alkaline hydrolysis of the C-S bonds of some of these compounds were reported[9,10]. Furthermore, the effect of various substituents of some of these sulfides and sulfones on toxicity[11], chemical shifts of methylene and aromatic protons[12–14], mass spectra[15], pK_a[16] and nucleophilic substitutions[17–19] were examined. The previous work has generated an interest in synthesizing new derivatives of the basic

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structure involving the N-alkyl phthalimido nucleus for chemical and biological studies. These compounds are N-[2-(4′-substituted phenylthio)ethyl] phthalimide la-g, N-[3-(4′-substituted phenylthio)propyl] phthalimide 2a-g and N-[4-(4′-substituted phenylthio)butyl] phthalimide 3a-g.

Generally compounds containing the CH_2-S moiety show low acidity of the α-hydrogen under basic conditions, while those containing more than one sulfide group enhances it[20]. This could be attributed to the formation of a carbanion intermediate which is stabilized by the 3d-orbital resonance.

RESULTS AND DISCUSSION

The structure of the title compounds were confirmed by UV, ^1H NMR and ^{13}CMR, Tables I-III. The IR spectra[21–23] (KBr pellets) for all compounds showed a sharp band at 1690–1705 cm^{-1} (C=O) and at 716–723 cm^{-1} (C-S). The mass spectra[23,24] of compounds 2a,b,e were studied. The assignments of the major fragment ion peaks of these compounds are compiled in Table IV and Scheme 1. The major role of the aliphatic n-propyl moiety is evident in directing the electron impact mass spectroscopic fragmentation pathways and this favors the formation of two successive ion series. The first includes the phthalimido ion peak at m/z 146 as well as the other ions at m/z 160, 174, 188 and 220. The second series of ions is characterized by the presence of the aryl part of the compound at m/z (M-220), (M-188), (M-174), (M-160) and (M-146) ions. The general behavior in the mass spectra of compounds 2a,b,e is characterized by the base peak formation in all compounds at m/z 160 which is formed via β-bond cleavage to the nitrogen atom giving rise to the formation of $[\text{phthalimido-}CH_2]^+$ ion, which is more favourable due to charge stabilization by resonance with the nitrogen atom.

Plots of the ^1H and ^{13}CMR δ ppm chemical shifts of the adjacent methylene protons and carbons to both sulfur and nitrogen atoms in all series against σ° constants[25] give good straight lines, Table V. The diminution in the transmission inductive effects of N-CH_2 relative to S-CH_2 is attributed to the proximity effect of the latter.

TABLE I Properties, UV, ^{1}H NMR and ^{13}CMR of N-[2-(4′ substituted phenylthio)ethyl] phthalimide 1a-g

Cpd. 1	R	MP °C	λ^a nm	ε/dm^1 mol^{-1} cm^{-1}	S % Found	^{1}H NMR (^{13}CMR) δ ppm in CDCl$_3$							
						$S-CH_2$ (t, 2H)	$N-CH_2$ (t, 2H)	$C_{3'',6''}$ (d, 2H)	$C_{4'',5''}$ (t, 2H)	$C_{2',6'}$ (d, 2H)	$C_{3',5'}$ (d, 2H)	$C_{4'}$ (t, 1H)	C = O
a^b	H	138	224.5	17170	10.98	3.45	3.58	7.88	7.58	7.46	7.33	7.26	---
			252.5	5860		(32.18	40.09	134.11	129.19	131.03	128.58	125.5	167.65)
b^c	CH_3	145	225	18780	10.52	3.06	3.53	7.80	7.58	7.36	7.18	--	---
			255	9130		(31.78	39.97	134.37	129.41	131.28	127.56	123.01	167.85)
c^d	OCH_3	132	227.5	19880	9.92	3.00	3.50	7.82	7.54	7.40	6.82	--	---
			253	1207		(31.68	39.77	133.78	130.06	132.28	128.54	115.53	169.81)
d^e	Cl	95	227.5	18330	9.89	3.33	3.69	7.42	7.28	7.82	7.82	--	---
			256	14410		(32.78	40.50	134.93	129.71	131.56	123.64	132.92	168.37)
e	Br	140	228	19680	8.56	3.29	3.65	7.85	7.55	7.39	7.47	--	---
			258	16160		(32.68	40.42	132.68	128.47	130.08	131.06	133.10	167.64)
f	NO_2	211	228.5	19880	9.56	3.68	3.84	7.92	7.54	7.58	8.16	--	---
			292	16550		(33.80	41.02	134.91	128.26	131.28	132.56	135.21	169.25)
										$C_{3',6'}$	$C_{4',5'}$	$C_{2'}$	
g^f	COOH	298	--	--	9.62	3.28	3.52	8.04	7.56	7.64	7.34	--	---
			--	--		(32.26	39.87	133.26	128.15	131.61	125.99	135.62	169.65

[a] In methanol. [b] $C_{3',5'}$ (t,2H); ^{13}CMR in DMSO. [c] 4′-CH_3 appear at δ_H 2.23 (s, 3H); δ_c 20.56 ppm. [d] 4′-OCH_3 appear at δ_H 3.78 (s, 3H); δ_C 55.51 ppm . [e] $C_{2',3',5',6'}$ (s, 4H). [f] 2′ -COOH; in acetone-d$_6$; OH appear at δ_H 11.12 (s, 1H); $C_{4',5'}$ (t, 2H).

TABLE II Properties, UV, ^{1}H NMR and ^{13}CMR of N-[3-(4′-substituted phenylthio) propyl] phthalimide 2a-g

Cpd. 2	*R*	*MP* °*C*	λ^a *nm*	*ε/dm*^{1} *mol*$^{-1}$ *cm*$^{-1}$	*S % Found*	^{1}*H NMR* (^{13}*CMR*) *δ ppm in CDCl*$_3$								
						2 CH$_2$ *(q, 2H)*	*S – CH*$_2$ *(t, 2H)*	*N – CH*$_2$ *(t, 2H)*	$c_{3'',6''}$ *(d, 2H)*	$C_{4'',5''}$ *(t, 2H)*	$C_{2',6'}$ *(d, 2H)*	$C_{3',5'}$ *(d, 2H)*	$C_{4'}$ *(t, 1H)*	*C = O*
a	H	88	225	18170	10.26	1.92	2.85	3.68	7.75	7.45	7.00 – 7.23 (m)			---
			253	8660		(27.62	30.67	40.68	134.58	129.29	131.24	128.32	126.5	169.26)
b^b	CH_3	81	225.5	18870	9.89	1.91	2.75	3.64	7.77	7.53	7.20	6.95	--	---
			256	9520		(27.26	30.18	40.61	133.92	128.96	131.18	127.12	125.23	169.12)
c^c	OCH_3	60	228.5	21570	9.58	1.91	2.70	3.61	7.72	7.46	7.24	6.71	--	---
			254	12170		(26.68	30.09	40.48	134.78	129.82	131.28	128.23	117.12	167.92)
d^d	Cl	90	227	19330	9.49	1.93	2.98	3.77	7.75	7.55	7.10	7.10	--	---
			261	14420		(27.28	31.20	41.02	133.62	129.62	132.54	125.92	127.31	167.12)
e	Br	103	228.5	19860	8.11	1.95	2.93	3.73	7.75	7.52	7.10	7.30	--	---
			262	16610		(27.65	31.08	40.96	133.98	128.56	129.86	131.32	127.85	169.64)
f	NO_2	212	229	19260	9.12	1.96	3.18	3.92	7.98	7.52	7.62	8.10	--	---
			295	15660		(28.12	32.52	44.50	134.98	129.10	131.28	132.78	128.53	169.58)
											$C_{3',6'}$	$C_{4',5'}$	$C_{2'}$	
g^e	COOH	170		--	9.18	1.92	2.91	3.81	7.98	7.54	7.76	7.32	--	---
				--		(27.21	33.12	38.78	134.98	128.38	131.68	127.12	129.52	169.12)

[a] In methanol. [b] 4′-CH_3 appear at δ_H 2.39 (s, 3H); δ_C 20.45 ppm. [c] 4′-OCH_3 appear at δ_H 3.66 (s, 3H); δ_C 55.45 ppm.
[d] $C_{2',3',5',6'}$ (s, 4H). [e] 2′-COOH; in acetone – d_6; OH appear at δ_H 11.21 (s, 1H); $C_{4',5'}$ (t, 2H).

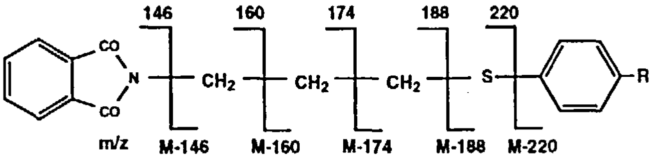
TABLE III Properties, UV, ^{1}H NMR and ^{13}CMR of N-[4-(4′-substituted phenylthio) butyl] phthalimide 3a-g

Cpd. 3	*R*	*MP °C*	λ^{a} *nm*	$\varepsilon/dm^{1}\ mol^{-1}\ cm^{-1}$	*S % Found*	^{1}H NMR (^{13}CMR) δ ppm in $CDCl_3$								
						2 C_{H2}(m, 4H)	S − CH_2(t, 2H)	N − CH_2(t, 2H)	$C_{3'',6''}$(d, 2H)	$C_{4'',5''}$(t, 2H)	$C_{2',6'}$(d, 2H)	$C_{3',5'}$(d, 2H)	$C_{4'}$(t, 1H)	C = O
a[b]	H	50	226.5	17770	10.0	1.72	2.90	3.65	7.75	7.50	7.21	7.12	6.95	---
			255	9830		(21.6	31.22	40.50	134.68	129.98	132.12	128.26	124.5	167.25)
b[c]	CH_3	75	227.5	19910	9.58	1.68	2.82	3.62	7.69	7.48	7.12	6.89	--	---
			256.5	10940		(22.12	30.99	40.41	133.89	129.24	131.21	128.12	123.12	169.10)
c[d]	OCH_3	67	229	20670	9.21	1.70	2.78	3.59	7.75	7.52	7.20	7.68	--	---
			257	11220		(21.89	30.51	40.25	134.98	129.32	132.68	127.15	118.2	169.12)
d[e]	Cl	80	226	14990	9.10	1.74	3.07	3.74	7.78	7.56	7.10	7.10	--	---
			261.5	7270		(22.12	31.92	40.78	133.68	129.72	132.12	128.15	125.48	167.12)
e	Br	95	227.5	19040	8.00	1.75	3.03	3.72	7.76	7.58	7.06	7.27	--	---
			262.5	16000		(21.26	31.74	40.70	134.68	128.68	130.70	131.02	125.69	169.12)
f	NO_2	158	229.5	19800	8.81	1.75	3.30	3.88	7.85	7.40	7.58	8.07	--	---
			293.5	16820		(22.21	33.12	41.28	134.51	128.62	131.32	132.68	127.11	169.52)
											$C_{3',6'}$	$C_{4',5'}$	$C_{2'}$	
g[f]	COOH	136	--	--	9.00	1.69	2.88	3.68	7.95	7.48	7.72	7.32	--	---
			--	--		(21.62	32.68	38.78	134.12	128.52	131.26	126.26	127.10	170.10)

[a] In methanol. [b] $C_{3',5'}$ (t,2H). [c] 4′-CH_3 appear at δ_H 2.22 (s, 3H); δ_C 20.12 ppm. [d] 4′-OCH_3 appear at δ_H 3.70 (s, 3H); δ_C 55.41 ppm . [e] $C_{2',3',5',6'}$ (s, 4H). [f] 2′ -COOH; in acetone − d_6; OH appear at δ_H 10.98 (s, 1H); $C_{4',5'}$ (t,2H).

TABLE IV Relative intensity of prominent peaks in the mass spectra of N-[3-(phenylthio) propyl] phthalimide 2a , N-[3-(4′-methylphenylthio) propyl] phthalimide 2b, N-[3-(4′-bromophenylthio) propyl] phthalimide 2e

Major peaks	*2a*		*2b*		*2e*	
	m/z	*rel.int. %*	*m/z*	*rel.int. %*	*m/z*	*rel.int %*
M^{+}.	297	37	311	25	375	1
M-220	77	46	91	53	155	< 1
220	220	< 1	220	< 1	220	< 1
M-188	109	42	123	85	187	8
188	188	95	188	58	188	13
M-174	123	9	137	< 1	201	3
174	174	4	174	< 1	174	< 1
M-160	137	4	151	< 1	215	< 1
160	160	100	160	100	160	100
M-146	151	<1	165	< 1	229	< 1
146	146	5	146	< 1	146	3



2a; R=H ($M^{+\cdot}$=297), 2b; R=CH_3($M^{+\cdot}$=311), 2e; R=Br($M^{+\cdot}$=375).

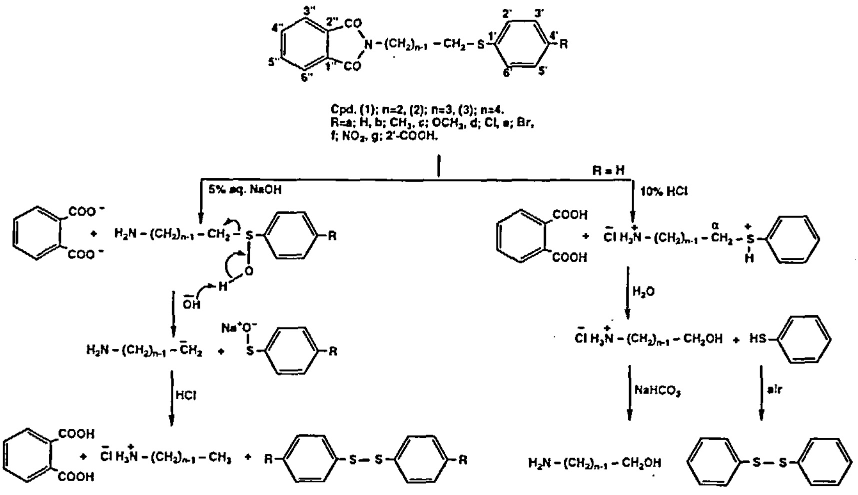
SCHEME 1

TABLE V Gradients of the correlated chemical shifts against σ° constants

Slope	*^{1}H NMR*		*^{13}CMR*	
Cpd.	*N-CH_2*	*S-CH_2*	*N-CH_2*	*S-CH_2*
1a-f	0.321 (r=0.997)	0.632 (r=0.993)	1.158 (r=0.996)	2.030 (r=0.995)
2a-f	0.287 (r=0.989)	0.447 (r=0.992)	0.953 (r=0.996)	2.440 (r=0.977)
3a-f	0.271 (r=0.997)	0.497 (r=0.999)	0.932 (r=0.991)	2.341 (r=0.991)

The alkaline hydrolysis of compounds la-f, 2a-f and 3a-f with 5% sodium hydroxide solution in dioxane gave a mixture of phthalic acid, diaryl disulfides[10] and alkylamines, Scheme 2. The gaseous ethylamine which has been generated during the alkaline hydrolysis reflux of compounds la-f was trapped with hydrochloric acid and identified as ethylamine hydrochloride[26]. n-Propylamine hydrochloride and n-butylamine hydrochloride obtained from the acidified filtrate of 2a-f and 3a-f respectively were identified by benzoylation process[27,28]. The acid hydrolysis of compounds la, 2a and 3a gave a mixture of phthalic acid, diphenyl disulfides[10] and hydroxylamines[29], Scheme 2. In the alkaline hydrolysis the C-S bond fission could be rationalized by the attack of the OH ion on the sulfur atom to give sodium aryl sulfene[10], rather than the α-carbanion formation[20], while the remaining moiety gives phthalate anion and alkyl amine, Scheme 2.

In the acid hydrolysis, the compounds are first protonated followed by a) hydrolysis to give phthalic acid. b) attack of H_2O on the α-carbon to give hydroxylamine and thiophenol. The latter undergoes air oxidation to give diphenyl disulfide, Scheme 2.



SCHEME 2

EXPERIMENTAL

Melting points are uncorrected, ^1H NMR and ^{13}CMR in acetone-d_6 or $CDCl_3$ were recorded using varian XL 300 spectrometer with Me_4Si as internal standard, IR spectra (KBr pellets) were measured on a Perkin-Elmer 1430 ratio recording infrared, UV spectra were recorded on a Shimadzu 160-A spectrophotometer and the mass spectra on MS 5988 spectrometer. Elemental analysis and mass spectra were carried out in the Faculty of Science, Cairo University, Egypt. The found analysis for carbon, hydrogen, nitrogen and sulfur were in excellent agreement with those calculated. Analytical Thin Layer Chromatography (TLC) was carried out on silica gel using (9.5:0.5) petroleum ether: ethylacetate, respectively.

General procedure for the synthesis of compounds 1, 2, 3a-g

N-(2-Bromoethyl)phthalimide, N-(3-bromopropyl)phthalimide and N-(4-bromobutyl)phthalimide (0.1 mole) in ethanol and the sodium salt of thiol compounds (Aldrich chemical Co. Inc) (0.1 mole) in ethanol were refluxed for 1–2h. Cooling, dilution and acidification with diluted hydrochloric acid gave a solid which was purified by recrystallization from aqueous ethanol.

Action of 5% sodium hydroxide solution

N-[Alkyl(4′-substituted phenylthio)]phthalimide la-g, 2a-f and 3a-f (lg) dissolved in dioxane and (10ml) of 5% sodium hydroxide solution were refluxed for 1h. On cooling and acidification a charactersitic thiol odor was detected. The reaction mixture was filtered. TLC of the precipitate indicated the presence of two compounds in all series which were seperated by column chromatography. The first separated compound was identified as 4,4′-disubstituted diphenyl disulfide[10] and the second compound in the mixture as phthalic acid (m.p. 210–11°C). The filtrate was vigorously shaken for 30 minutes with a mixture of 2 ml benzoyl chloride and 5 ml of 10% sodium hydroxide solution, then diluted with cold water. Series 2a-f and 3a-f gave a precipitate which was identified as N-(n-propyl)benzamide (m-p. 84°C, lit.[27] 83°C) and N-(n-butyl)benzamide (m.p.42°C, lit[28]. 42°C). The gaseous ethylamine generated during the reflux of series 1a-f was trapped by hydrochloric acid and identified as ethylamine hydrochloride (m.p.78°C, lit[26].76–78°C). All of these compounds were confirmed by comparing their melting points and ^{1}H NMR spectra with a commercial specimen.

Action of 10% aqueous hydrochloric acid

N-[Alkyl(phenylthio)]phthalimide 1a, 2a and 3a (1g) dissolved in dioxane and (10 ml) of 10% aqueous hydrochloric acid were refluxed for lh. On cooling and dilution a charactersitic thiophenol odor was detected. The reaction mixture was filtered and the precipitate was chromatographically separated to phthalic acid (m.p. 210°C) and diphenyl disulfide (m.p. 61°C, lit[10]. 60°C). The filtrate was treated with aqueous $NaHCO_3$ and extracted with ether. Evaporation of the ether layer gave an oil in all series (n_D^{20} =1.46) which was identified by ^1H NMR as ethanolamine[29], 3-amino-1-propanol[29] and 4-amino-l-butanol[29], respectively.

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