[Chem. Pharm. Bull. 28(1) 126—133 (1980)]

Chlorinolyses of Alkyl (or Aryl) Phthalimidomethyl Sulfides with Sulfuryl Chloride or Chlorine in the Presence[1] and the Absence[2] of Acetic Anhydride

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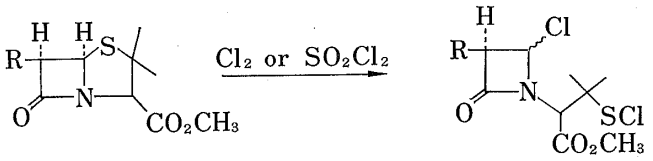
Alkyl and aryl phthalimidomethyl sulfides give alkane- and arenesulfenyl chlorides on reaction with equimolar sulfuryl chloride or molecular chlorine in an aprotic solvent at room temperature, but give alkane- and arenesulfinyl chlorides on reaction with two molar equivalents of the same reagent in the presence of acetic anhydride under the same conditions. The utility of these reactions for the synthesis of organo sulfenyl chlorides and sulfinyl chlorides was confirmed.

Keywords——chlorinolysis; oxidative cleavage; alkyl (or aryl) phthalimidomethyl sulfide; alkane (or arene) sulfenyl chloride; alkane (or arene) sulfinyl chloride; 2-chloroalkyl sulfides; α,β-unsaturated sulfides

An earlier paper[4] from this laboratory reported that alkyl and aryl phthalimidomethyl sulfoxides can be converted into alkane- and arenesulfinyl chlorides by the action of sulfuryl chloride or molecular chlorine in an aprotic solvent. In continuing studies with the sulfide precursors of alkyl and aryl phthalimidomethyl sulfoxides, it was found that the sulfides give alkane- and arenesulfenyl chlorides on reaction with equimolar amounts of sulfuryl chloride or molecular chlorine in an aprotic solvent at room temperature, and alkane- and arenesulfinyl chloride on reaction with two molar equivalents of the same reagent in the presence of acetic anhydride under the same conditions. Both reactions are described in the present paper, and should be useful for the synthesis of organic sulfenyl chlorides and sulfinyl chlorides.

Very recently, after our experimental work had been completed, a paper relating to the former reaction was published,[5] which dealt with the chlorinolysis of N-[α-(phenylthio)-alkyl]phthalimides with sulfuryl chloride, and nongeneralized path is also available for the special case of penicillin derivatives.[6]



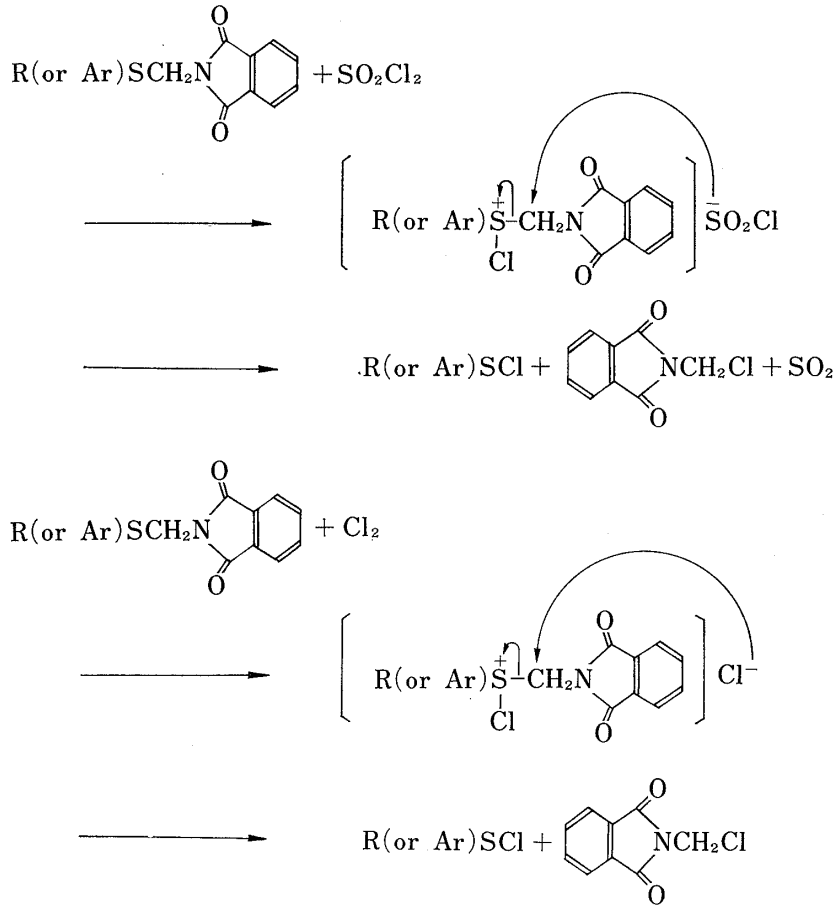
R=phthalimido-

1. Alkane- or Arenesulfenyl Chlorides

Pentyl and phenyl phthalimidomethyl sulfides reacted with equimolar amounts of sulfuryl chloride and of chlorine in carbon tetrachloride at room temperature to give pentane-

1) This work was presented at the 98th Annual Meeting of the Pharmaceutical Society of Japan, Okayama, April 1978.
2) This work was presented at the 99th Annual Meeting of the Pharmaceutical Society of Japan, Sapporo August 1979.
3) Location: 2-2-1 *Oshika, Shizuoka-shi 422, Japan.*
4) M. Uchino, K. Suzuki, and M. Sekiya, *Chem. Pharm. Bull.*, **27**, 1199 (1979).
5) J.W. Worley, *J. Org. Chem.*, **44**, 1178 (1979).
6) S. Kukolja, *J. Am. Chem. Soc.*, **93**, 6267 (1971).

sulfenyl chloride and benzenesulfenyl chloride, which were converted into diethylamide derivatives in yields of 30—37% and 70—83%, respectively. The reaction pathways may be as follows. Because of their great lability (especially alkanesulfenyl chlorides) as regards



disproportionation and hydrolysis in air, it is rather difficult to isolate these compounds from the reaction solution. Therefore, from a preparative standpoint, we intended to use the reaction solutions as sources of organic sulfenyl chloride without isolation. The reaction with olefins was conducted by direct addition to the reaction mixture obtained by the reaction of alkyl and phenyl phthalimidomethyl sulfides with sulfuryl chloride. For example as a typical procedure, pentyl phthalimidomethyl sulfide was reacted with equimolar sulfuryl chloride in carbon tetrachloride and then cyclohexene was added to the resulting reaction solution with ice cooling. This procedure gave 2-chlorocyclohexyl pentyl sulfide in 68% yield, which is higher than that of the intermediate pentanesulfenyl chloride isolated. This *in situ* olefinic addition of the sulfenyl chloride was extensively examined and a practical procedure was developed, as summarized in Table I. Except for 2-chlorocyclohexyl phenyl sulfide, all the 2-chloroalkyl sulfides obtained have not been described previously; they gave satisfactory microanalyses and the expected nuclear magnetic resonance (NMR) and infrared (IR) spectra (see Table II). The distribution of isomeric adducts on sulfenyl chloride addition to unsymmetrical olefins is known to be rather complicated, being governed by a kinetically controlled reaction involving functional group activation and steric factors, and subsequent thermodynamically controlled rearrangement.[7] Structural analyses of the adducts of styrene and α-methylstyrene, which were obtained as single isomers, were carried out by converting them to the corresponding α,β-unsaturated sulfides by reaction with *tert*-butoxide in tetrahydrofuran (THF).

7) W.A. Thaler, W.H. Mueller, and P.E. Butler, *J. Am. Chem. Soc.*, **90**, 2069 (1968).

$$CH_3(CH_2)_4SCH_2\underset{Cl}{\underset{|}{C}}HC_6H_5 \xrightarrow[\text{in THF}]{tert.\text{-BuOK}} CH_3(CH_2)_4SCH{=}CHC_6H_5$$

$$CH_3(CH_2)_4SCH_2\underset{Cl}{\underset{|}{\overset{CH_3}{\overset{|}{C}}}}C_6H_5 \xrightarrow[\text{in THF}]{tert.\text{-BuOK}} CH_3(CH_2)_4SCH{=}\overset{CH_3}{\overset{|}{C}}C_6H_5$$

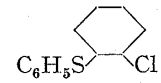
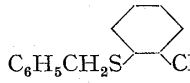
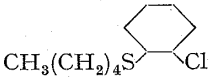
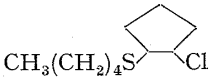
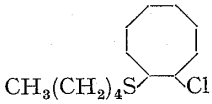
The adduct of methyl vinyl ketone was assigned as a similar Markovnikov product **1** by analysis of its NMR spectrum based on previously reported work[7] dealing with NMR analysis of isomeric adducts of methanesulfenyl chloride to olefins conjugated with CO_2R, COCl, $CONH_2$, CN and COR. It was reported that the region of the methylene protons next to sulfur and the methine proton next to chlorine exhibits an ABX system in one isomer, in contrast to an ABC system in another isomer. The ABX chemical shifts of the product **1**, shown in Table II, are very close to the reported values for analogous isomers.

$$CH_2{=}CHCOCH_3 \xrightarrow{CH_3(CH_2)_4SCl} CH_3(CH_2)_4SCH_2\underset{Cl}{\underset{|}{C}}HCOCH_3$$

1

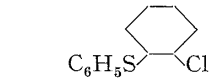
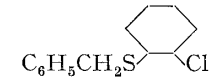
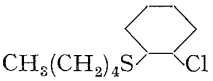
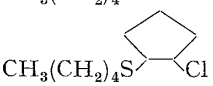
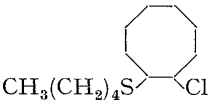
On the other hand, the *anti*-Markovnikov structure **2** may be assigned for the adduct of methacrylonitrile on the basis of the previous work[7] in which exclusive production of *anti*-Markovnikov adducts of methanesulfenyl chloride was reported with such olefins conjugated with nitrile.

Table I. Reaction of Olefins with Sulfenyl Chlorides formed *in situ* from Phthalimidomethyl Sulfides

R (or Ar)	Olefin	Reaction time (hr)	Product	Yield (%)
C_6H_5–		0.5		93
$C_6H_5CH_2$–		0.5		65
$CH_3(CH_2)_4$–		0.5		68
$CH_3(CH_2)_4$–		0.5		65
$CH_3(CH_2)_4$–		0.5		42
$CH_3(CH_2)_4$–	$CH_2{=}CHC_6H_5$	0.5	$CH_3(CH_2)_4SCH_2\underset{Cl}{\underset{\|}{C}}HC_6H_5$[a]	66
$CH_3(CH_2)_4$–	$CH_2{=}\overset{CH_3}{\overset{\|}{C}}C_6H_5$	0.5	$CH_3(CH_2)_4SCH_2\underset{Cl}{\underset{\|}{\overset{CH_3}{\overset{\|}{C}}}}C_6H_5$[a]	62
$CH_3(CH_2)_4$–	$CH_2{=}CHCOCH_3$	0.5	$CH_3(CH_2)_4SCH_2\underset{Cl}{\underset{\|}{C}}HCOCH_3$	72
$CH_3(CH_2)_4$–	$CH_2{=}C(CH_3)CN$	3	$CH_3(CH_2)_4S\underset{CN}{\underset{\|}{C}}(CH_3)CH_2Cl$	63

a) This adduct was identified by conversion into α,β-unsaturated sulfide.

Table II. Physical, Spectral and Analytical Data for the Adducts

Adduct	bp (°C) (mmHg)	NMR (δ in $CDCl_3$) $-CH_nCl-$	NMR (δ in $CDCl_3$) $-SCH_n-$	Analysis Calcd (Found) C	Analysis Calcd (Found) H
	119—121 (0.01)	4.25—3.78 1H, m	3.54—3.08 1H, m	63.56 (63.11	6.67 6.39)
	109—110 (0.02)	4.21—3.98 1H, m	3.00—2.60 1H, m	64.84 (65.02	7.12 7.15)
	99—102 (0.05)	4.28—3.90 1H, m	3.10—2.65 1H, m	59.84 (59.98	9.59 9.98)
	72— 75 (0.06)	4.38—4.05 1H, m	3.50—3.05 1H, m	58.23 (58.02	9.26 9.41)
	97—100 (0.04)	4.32—4.02 1H, m	3.20—2.84 1H, m	62.74 (62.79	10.13 9.98)
$CH_3(CH_2)_4SCH_2\underset{\displaystyle Cl}{\underset{\vert}{C}}HCOCH_3$	86— 88 (0.01)	4.34, 1H ABXq ($J_{AX}=8$, $J_{BX}=6$)	3.14, 1H, dd 2.86, 1H, dd ($J_{gem}=14$, $J_{vic}=8, 6$)	51.78 (51.68	8.21 8.09)
$CH_3(CH_2)_4S\underset{\displaystyle CN}{\underset{\vert}{C}}CH_2Cl$[a]	87— 90 (0.10)	3.50, 1H, d ($J=12$) 3.88, 1H, d ($J=12$)		52.54 (52.50	7.84 7.85)

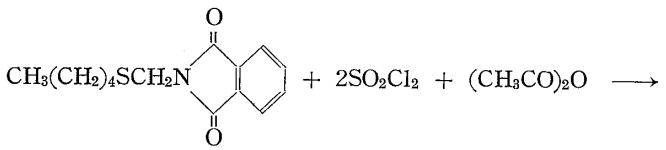
a) Nitrogen and chlorine analyses, Calcd for $C_9H_{16}ClNS$: N, 6.81; Cl, 17.28. Found: N, 6.35; Cl, 17.06.

$$CH_2{=}C(CH_3)CN \xrightarrow{CH_3(CH_2)_4SCl} ClCH_2\underset{\displaystyle S(CH_2)_4CH_3}{\underset{\vert}{C}}(CH_3)CN$$

2

2. Alkane- or Arenesulfinyl Chlorides

We have found that by allowing alkyl and aryl phthalimidomethyl sulfides to react with two molar equivalents of sulfuryl chloride or chlorine in the presence of acetic anhydride in an aprotic solvent, oxidative cleavage proceeds smoothly at room temperature to give alkane- and arenesulfinyl chlorides. This procedure is preferrable to that previously reported for sulfinyl chloride production from the sulfoxides.[4] The initial experiment was conducted with pentyl phthalimidomethyl sulfide. A typical procedure and the solvent effect in the reaction with sulfuryl chloride are summarized in Table III; the highest yield (69—71%) of pentanesulfinyl chloride was obtained with benzene or carbon tetrachloride as a solvent. The reaction can be expressed by the following equation. Isolation of pentanesulfinyl chloride,



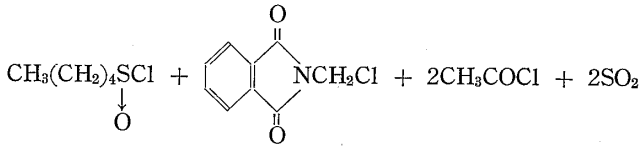
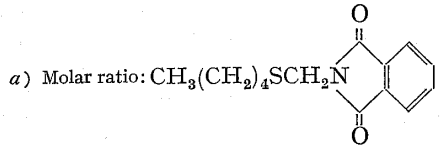


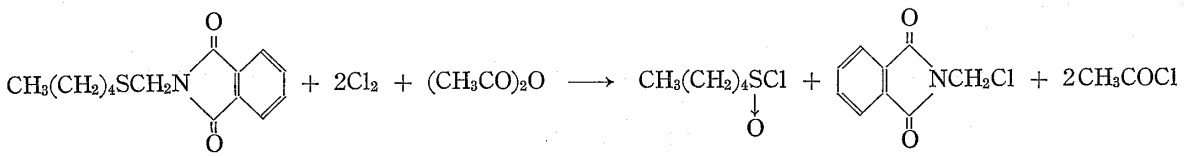
Table III. Solvent Effect[a]

Solvent	Reaction time (hr)	Yield (%)[b]
CCl_4	0.5	71
Benzene	0.5	69
$CHCl_3$	0.5	48
iso-Pr_2O	1.5	7
Petr. ether	0.5	0

a) Molar ratio:  : SO_2Cl_2: $(CH_3CO)_2O$=1 : 2.2 : 1.

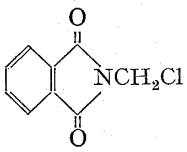
b) Yields of pentanesulfinylanilide, to which the sulfinyl chloride was converted.

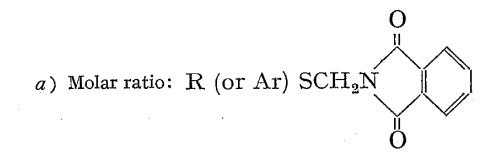
the formation of which was confirmed by its conversion into the anilide, was achieved simply by removal of the solvent along with acetyl chloride, which was detected by means of its methyl proton signal in NMR measurement, from the reaction solution, followed by extraction of the chloride with petroleum ether, when N-(chloromethyl)phthalimide separated as an insoluble material. In place of sulfuryl chloride, chlorine can be used. Using a similar procedure, the reaction with chlorine proceeded in carbon tetrachloride at room temperature to give pentanesulfinyl chloride in 71% yield as the anilide.



The reaction with sulfuryl chloride and with chlorine were investigated with various alkyl and aryl phthalimidomethyl sulfides. The results are summarized in Tables IV and V, and show the reactions to be useful for synthesizing organic sulfinyl chlorides. N-(chloro-

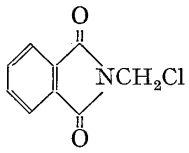
Table IV. Reaction with SO_2Cl_2[a]

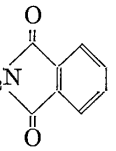
R (or Ar)	Reaction time (hr)	Yield (%)	
		R (or Ar) SCl[b] (O)	
$CH_3(CH_2)_4$–	0.5	71	90
$CH_3(CH_2)_7$–	0.5	40	95
$CH_3(CH_2)_{11}$–	1.0	31	97
C_6H_{11}–	1.0	27	99
$C_6H_5CH_2$–	1.0	50	99
p-$CH_3C_6H_4$–	0.5	15	97

a) Molar ratio: R (or Ar)  : SO_2Cl_2: $(CH_3CO)_2O$=1 : 2.2 : 1.

b) Yield of anilide, to which the sulfinyl chloride was converted.

Table V. Reaction with Cl_2[a]

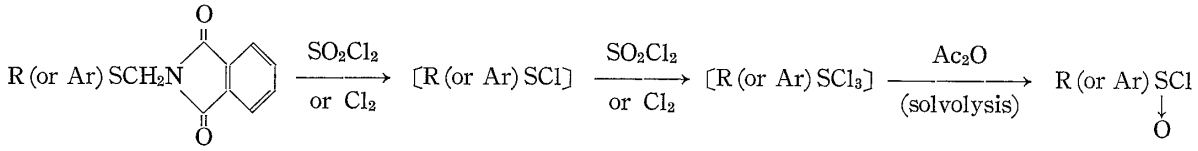
R (or Ar)	Reaction time (hr)	Yield (%) R (or Ar) SCl[b] (O)	Yield (%) 
$CH_3(CH_2)_4$–	0.5	71	87
$CH_3(CH_2)_7$–	0.5	81	92
$CH_3(CH_2)_{11}$–	0.5	94	95
$CH_3(CH_2)_{13}$–	0.5	93	82
C_6H_{11}–	0.5	67	95
$C_6H_5CH_2$–	0.5	59	99
C_6H_5–	0.5	70	95
p-$CH_3C_6H_4$–	0.5	89	99
p-ClC_6H_4–	0.5	87	97
p-$NO_2C_6H_4$–	2.0	53	95
β-$C_{10}H_7$–	0.5	79	92

a) Molar ratio: R (or Ar)  : Cl_2 : $(CH_3CO)_2O$ = 1 : 2.2 : 1.

b) Yield of anilide, to which the sulfinyl chloride was converted.

methyl)phthalimide, obtained as a by-product, can be reused for synthesizing the starting phthalimidomethyl sulfides.

It is apparent that sulfinyl chloride production proceeds through a sulfenyl chloride intermediate. The formation of the sulfinyl chloride from the sulfenyl chloride intermediate may proceed in the way described previously for sulfinyl chloride formation from alkyl or aryl disulfides on chlorinolysis in the presence of acetic anhydride;[8] it was suggested that an intermediate sulfenyl chloride is first chlorinated to an organosulfur trichloride and subsequently solvolyzed by acetic anhydride to the sulfinyl chloride.



Experimental[9]

Material——The preparation of alkyl (or aryl) phthalimidomethyl sulfides was described in the preceding paper.[4]

Pentane- and Benzenesulfenyl Chlorides General Procedure

Method A: Reaction with Sulfuryl Chloride——Sulfuryl chloride (3.0 g, 0.022 mol) was added dropwise at room temperature to a solution or suspension of 0.02 mol of pentyl or phenyl phthalimidomethyl sulfide

8) I.B. Douglass and R.V. Norton, *J. Org. Chem.*, 33, 2104 (1968).

9) All melting points and boiling points are uncorrected. IR spectra were recorded on a Hitachi EPI-G2 spectrophotometer. NMR spectra were taken with a Hitachi R-24 spectrophotometer (60 MHz). Chemical shift values are given in δ (ppm) relative to tetramethylsilane as an internal standard. The following abbreviations are used: s=singlet, d=doublet, dd=doublet of doublets, t=triplet, q=quartet, m=multiplet.

in 60 ml of carbon tetrachloride. In the run with phenyl phthalimidomethyl sulfide, the initial heterogeneous mixture became homogeneous during the course of the reaction, whereas in the run with pentyl analog the reaction started homogeneously. A part of the N-(chloromethyl)phthalimide precipitated at the end of the reaction and was collected by filtration. The filtrate was concentrated under reduced pressure. Pentane- or benzenesulfenyl chloride was extracted from the resulting residue with petroleum ether and was converted into the corresponding sulfenyldiethylamide by addition of diethylamine to the petroleum ether solution. Benzenesulfenyl diethylamide, bp 79—81° (1 mmHg), yield, 70%, was identified by comparison of its IR spectrum with that of an authentic specimen. Pentanesulfenyl diethylamide, bp 64—65° (4 mmHg), yield, 37%. *Anal.* Calcd for $C_9H_{21}NS$: C, 61.65; H, 12.01; N, 7.99. Found: C, 61.92; H, 11.99; N, 8.00.

Additional N-(chloromethyl)phthalimide was obtained as a petroleum ether-insoluble powder, which was collected and recrystallized from AcOEt. Prisms, mp 132—134° (lit.[10] mp 134°), overall yield, 95—97%.

Method B: Reaction with Chlorine——Chlorine (1.6 g, 0.022 mol) dissolved in 30 ml of carbon tetrachloride was added dropwise at room temperature to a solution or suspension of 0.02 mol of pentyl or phenyl phthalimidomethyl sulfide in 30 ml of carbon tetrachloride. A part of the N-(chloromethyl)phthalimide precipitated at the end of the reaction was collected by filtration. Treatment of the filtrate by a procedure similar to that described in method A gave pentanesulfenyl chloride (yield, 30% as the diethylamide) and benzenesulfenyl chloride (yield, 83% as the diethylamide), respectively, and N-(chloromethyl)phthalimide in 97—99% overall yield. Identification of the sulfenyl chlorides was carried out as in method A.

Reaction of Alkane (or Arene)sulfenyl Chlorides with Olefins General Procedure——Sulfuryl chloride (2.7 g 0.02 mol) was added dropwise at room temperature to a solution or suspension of 0.02 mol of alkyl (or aryl) phthalimidomethyl sulfide in 50 ml of carbon tetrachloride. Stirring was continued until the starting sulfide had disappeared on TLC (silica gel–benzene), then 0.026 mol of olefin was added dropwise at 0°. The reaction mixture was stirred until the sulfenyl chloride color was quenched. A part of the N-(chloromethyl)-phthalimide deposited in the course of the reaction and was collected by filtration. The filtrate was concentrated under reduced pressure. The sulfenyl chloride adduct was extracted from the resulting residue with petroleum ether and was distilled after removal of the petroleum ether by evaporation. Additional N-(chloromethyl)phthalimide was obtained as a petroleum ether–insoluble powder. The reaction times and yields of the products are shown in Table I. Spectral and analytical data for the adducts are listed in Table II.

Styrene and α-methylstyrene adducts were identified by converting them into the corresponding α,β-unsaturated sulfides by the following procedures. Potassium tertiary butoxide (4.5 g, 0.04 mol) was added to a solution of 0.02 mol of the adduct obtained in 50 ml of THF and the reaction mixture was refluxed for 2 hr. After cooling, carbon dioxide was bubbled into the reaction mixture for 0.5 hr. The reaction mixture was concentrated under reduced pressure and the resulting residue was extracted with benzene. The benzene layer obtained above was washed with water and dried over $MgSO_4$. After removal of the benzene, the corresponding α,β-unsaturated sulfide was obtained by distillation of the residue. Pentyl styryl sulfide, bp 118° (0.03 mmHg). NMR (δ in $CDCl_3$): 7.60—7.00 (5H, m, aromatic protons), 6.74 (1H, d, J=15 Hz, PhC<u>H</u>=CH–), 6.38 (1H, d, J=15 Hz, PhCH=C<u>H</u>–), 2.74 (2H, t, J=7 Hz, –SCH_2–), 0.90 (3H, t, J=6 Hz, –CH_3). *Anal.* Calcd for $C_{13}H_{18}S$: C, 75.67; H, 8.79. Found: C, 75.74; H, 8.79. Pentyl α-methylstyryl sulfide, bp 110° (0.02 mmHg). NMR (δ in $CDCl_3$): 7.50—7.04 (5H, m, aromatic protons), 6.29 (1H, s, –C<u>H</u>=C(CH_3)–), 2.77 (2H, t, J=7 Hz, –SCH_2–), 2.10 (3H, s, –CH=C(C<u>H</u>$_3$)–), 0.89 (3H, t, J=6 Hz, terminal CH_3). *Anal.* Calcd for $C_{14}H_{20}S$: C, 76.30; H, 9.15. Found: C, 76.55; H, 9.07.

Alkane(or Arene)sulfinyl Chloride General Procedure

Method A: Reaction with Sulfuryl Chloride——Sulfuryl chloride (5.9 g, 0.044 mol) was added dropwise to a stirred solution of 0.02 mol each of alkyl (or aryl) phthalimidomethyl sulfide and 2.0 g (0.02 mol) of acetic anhydride in 60 ml of carbon tetrachloride at room temperature, and stirring was continued until the starting material had disappeared. In the runs with benzyl phthalimidomethyl sulfide and *p*-tolyl phthalimidomethyl sulfide, the initial heterogeneous reaction mixture became homogeneous during the course of the reaction. At the end of the reaction, a part of the N-(chloromethyl)phthalimide deposited and was collected by filtration. The filtrate was concentrated under reduced pressure. Alkane(or arene)sulfinyl chloride was extracted from the resulting residue with several portions of petroleum ether, and addition of aniline to the petroleum ether solution converted the product into sulfinyl anilide. The IR spectra of the anilides obtained, which have appeared in the literature[4] except for that of octanesulfinyl chloride, showed good correspondence with those of authentic specimens. Octanesulfinyl anilide, mp 84—86°. Needles (MeOH). IR ν_{max}^{KBr} (cm^{-1}): 3170 (>NH), 1042 (>S→O). NMR (δ in $CDCl_3$): 7.40—6.75 (5H, m, aromatic protons), 7.74 (1H, bs, >NH), 2.98 (2H, t, J=8 Hz, –S(O)CH_2), 2.10—1.02 (12H, m, –$(CH_2)_6$–), 0.86 (3H, t, J=5 Hz, CH_3–). *Anal.* Calcd for $C_{14}H_{23}NOS$: C, 66.36; H, 9.15; N, 5.53. Found: C, 66.45; H, 9.30; N, 5.47.

Additional N-(chloromethyl)phthalimide was obtained as a petroleum ether-insoluble powder.

Reaction times and yields of the products are listed in Table IV.

Method B: Reaction with Chlorine——A solution of 3.1 g (0.044 mol) of chlorine dissolved in 50 ml of carbon tetrachloride was added dropwise with stirring to a mixture of 0.02 mol each of alkyl (or aryl) phtha-

10) H. Böhme and A. Müller, *Arch. Pharm.*, **296**, 54 (1964).

limidomethyl sulfide and 2.0 g (0.02 mol) of acetic anhydride in 10 ml of carbon tetrachloride at room temperature. In the runs with tetradecyl phthalimidomethyl sulfide, benzyl phthalimidomethyl sulfide and aromatic analogs, the heterogeneous mixture became homogeneous during the course of the reaction, whereas in the runs with other sulfides, the reaction started homogeneously. A part of the N-(chloromethyl)phthalimide deposited in the reaction solution and was collected by filtration. Treatment of the filtrate by a procedure similar to that described in method A gave alkane(or arene)sulfinyl chloride and additional N-(chloromethyl)-phthalimide. Sulfinyl chlorides obtained were identified by conversion to the corresponding anilides. IR spectra of the anilides obtained, which have appeared in the literature[4] except for that of tetradecanesulfinyl anilide, showed good correspondence with those of authentic specimens. Tetradecanesulfinyl anilide, mp 85—87°. Prisms (MeOH). IR ν_{max}^{KBr} (cm^{-1}): 3170 (>NH), 1040 (>S→O). NMR (δ in $CDCl_3$): 7.34 (1H, bs, >NH), 7.30—6.86 (5H, m, aromatic protons), 2.98 (2H, t, J=8 Hz, $-S(O)CH_2$), 2.02—1.05 (24H, m, $(CH_2)_{12}$–), 0.86 (3H, t, J=5 Hz, CH_3–). *Anal.* Calcd for $C_{20}H_{35}NOS$: C, 71.16; H, 10.45; N, 4.15. Found: C, 70.69; H, 10.54; N, 4.11.

Reaction times and yields of the products are listed in Table V.

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