BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN, VOL. 45, 866—870(1972)

Sulfenylation of Active Methylene Compounds with Sulfenamides

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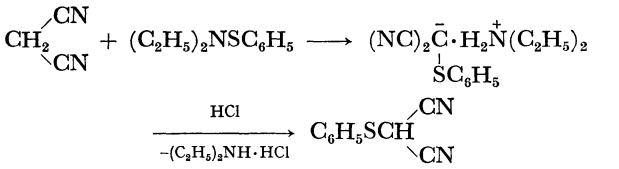
(Received July 21, 1971)

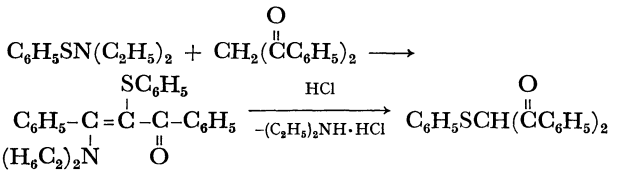
Equimolar reactions of sulfenamides derived from secondary alkylamines with active methylene compounds afforded mono-sulfenylated compounds in good yields. The reactions of 2 mol of sulfenamides derived from imides with 1 mol of active methylene compounds in the presence of a base gave di-sulfenylated compounds. It was found that α-mono-sulfenylated ketones were prepared by the reactions of enamines with sulfenamides derived from imides. α-*gem*-Di-sulfenylated ketones were prepared by the reactions of α-mono-sulfenylated ketones with sulfenamides derived from imides in the presence of a base. The preparation and reactions of *N*-phenylthiobenzamidine hydrochloride were also examined.

In a previous communication,[1] sulfenylation of active methylene compounds by the use of sulfenamides was reported. The reactions are described more in detail with new results in this paper.

It was found that the equimolar reaction of *N,N*-diethylbenzenesulfenamide with malononitrile in methylene chloride at room temperature for 5 hr resulted in the formation of the dimethylammonium salt of phenylthiomalononitrile in 55% yield. By acid hydrolysis of the salt, phenylthiomalononitrile was obtained in quantitative yield.



In the case of the reaction of *N,N*-diethylbenzenesulfenamide with dibenzoylmethane, α-phenylthio-β-*N,N*-diethylaminochalcone was obtained in 66% yield instead of the salt. The enamine was converted into phenylthiodibenzoylmethane in quantitative yield by acid hydrolysis.



The reactions of *N,N*-diethylbenzenesulfenamide with acetylacetone, ethyl acetoacetate or ethyl malonate under similar conditions without isolation of the intermediates, enamines or salts, afforded corresponding mono-sulfenylated products in good yields (Table 1).

The reactions of *N*-phenylthiopyrrolidine with active methylene compounds were examined. Treatment of *N*-phenylthiopyrrolidine with ethyl acetoacetate at room temperature, followed by acid hydrolysis gave ethyl acetyl(phenylthio)acetate in 60% yield. Similarly, ethyl phenylthiomalonate was obtained in 52% yield by the reaction of *N*-phenylthiopyrrolidine with ethyl malonate. The yields of the mono-sulfenylated products by the above mentioned reactions are higher than those of the reactions of active methylene compounds with *N,N*-diethylbenzenesulfenamide. The results suggest that the reactivity of the sulfenamides depends on the basicity of the amino component of the sulfenamides.

In order to clarify the effects of the amino component of the sulfenamide on this type of sulfenylation, the reactions of ethyl malonate with various sulfenamides such as *N*-phenylthioaniline, *N*-phenylthiopiperidine or *N*-phenylthiobenzamidine[2] were examined (Table 2). The results show that neither *N*-phenylthioaniline, derived from a weak base, nor *N*-phenylthiobenzamidine derived from a strong base, affords a sulfenylated compound. *N,N*-diethylbenzenesulfenamide, *N*-phenylthiopyrrolidine or *N*-phenylthiopiperidine is suitable for mono-sulfenylation of active methylene compounds.

On the other hand, it was found that di-sulfenylated products were obtained by the reactions of *N*-phenylthiosuccinimide with active methylene compounds in the presence of a base. For example, when 2 mol of *N*-phenylthiosuccinimide, 1 mol of dibenzoylmethane and 2 mol of triethylamine were stirred overnight in methylene chloride at room temperature, bis(phenylthio)dibenzoylmethane was obtained in 50% yield.

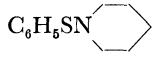
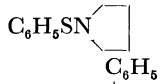
1) T. Mukaiyama, S. Kobayashi and T. Kumamoto, *Tetrahedron Lett.*, **1970**, 5115.

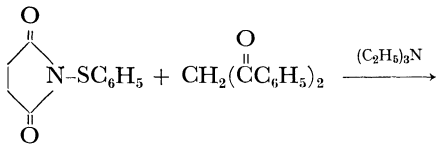
2) J. Goerdeler, D. Krause-Loevenich and B. Wedekind, *Chem. Ber.*, **90**, 1638 (1957).

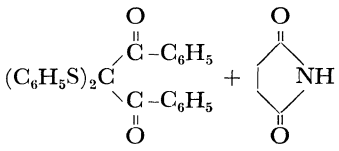
Table 1. Reactions of *N,N*-diethylbenzene sulfenamide with active methylene compounds

$CH_2{<}^{X}_{Y}$	Yield (%)	Bp (°C/mmHg) or mp [°C]	Elemental analysis (%) Found C	Found H	Found S	Calcd C	Calcd H	Calcd S
$CH_2(COC_6H_5)_2$	66	[93—94]	76.13	4.98	9.86	75.89	4.85	9.63
$CH_2(COCH_3)_2$	77	(152—153/22)	63.62	5.78	15.48	63.45	5.81	15.37
$CH_2(CN)_2$	55	[84—87]	62.37	3.37	18.67	62.07	3.47	18.37
$CH_3COCH_2CO_2C_2H_5$	37	(125—127/4.5)	60.33	6.05	13.30	60.50	5.92	13.43
$CH_2(CO_2C_2H_5)_2$	48	(148 1.7)	58.01	5.99	12.07	58.20	6.01	11.93

Table 2. Reactions of ethyl malonate with sulfenamides

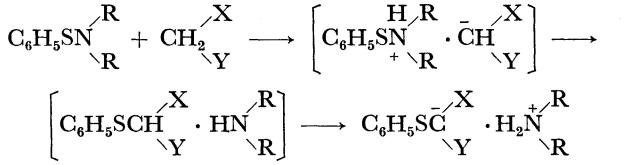
Sulfenamide	Yield of $C_6H_5SCH(CO_2C_2H_5)_2$ (%)
$C_6H_5SNHC_6H_5$	—
$C_6H_5SN(C_2H_5)_2$	48
	44
	52
$C_6H_5SN{=}C(C_6H_5){-}NH_2$	—



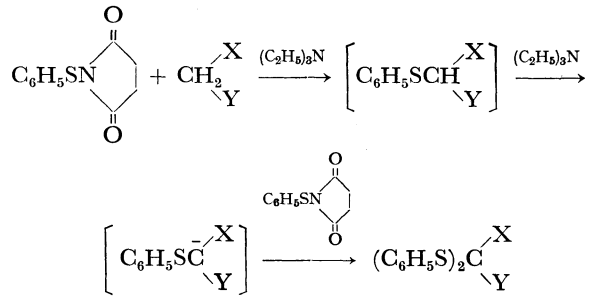


In a similar way, the reactions of *N*-phenylthiosuccinimide with acetylacetone, malononitrile, ethyl acetoacetate or ethyl malonate afforded the corresponding di-sulfenylated products in good yields (Table 3).

The results can be explained as follows. Sulfenylation of active methylene compounds with the sulfenamide derived from the secondary alkylamines would proceed through the activation of sulfur-nitrogen bond by the protonation to the nitrogen atom, followed by the reaction on the sulfur atom with active methylene compounds to give mono-sulfenylated products. These would be converted rapidly to enamines or salts by the subsequent reactions with the secondary alkylamines formed at the same time. Since enamines or salts can not participate in the activation of the sulfenamides, di-sulfenylated products would not be produced in these reactions.



In the case of sulfenylation by the use of sulfenamides derived from imides, the sulfenamide can react with active methylene compounds in basic media to produce sulfenylated products owing to a labile elimination of stable imide anions from the sulfenamides. Thus, the initially formed triethylammonium salts of mono-sulfenylated products further react with sulfenamides to give di-sulfenylated products.



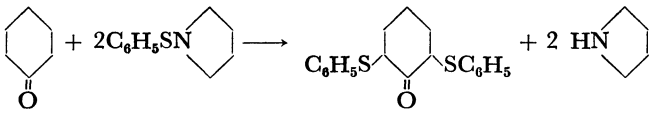
Sulfenylation of the α-carbon of ketones by the use of the above mentioned sulfenamides was next tried in order to establish a convenient method for the preparation of α-mono or α-*gem*-di-sulfenylated ketones considered to be valuable as synthetic intermediates. When *N,N*-diethylbenzenesulfenamide was allowed to react with cyclohexanone in methylene chloride, no sulfenylated product was obtained and only starting materials

Table 3. Reactions of *N*-phenylthiosuccinimide with active methylene compounds

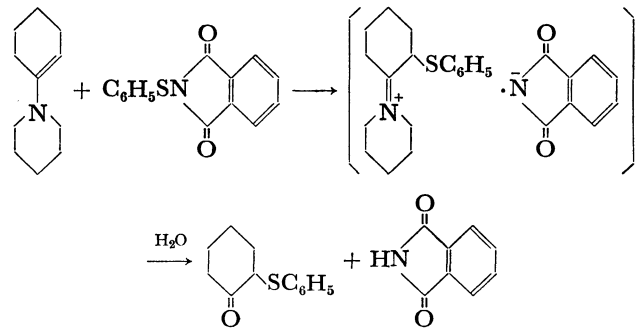
$CH_2{<}^{X}_{Y}$	Yield (%)	Mp (°C)	Elemental analysis (%) Found C	Found H	Found S	Calcd C	Calcd H	Calcd S
$CH_2(COC_6H_5)_2$	50	184.5—185.5	73.41	4.87	14.39	73.63	4.58	14.53
$CH_2(COCH_3)_2$	73	117—118	64.72	5.21	19.99	64.55	5.10	20.23
$CH_2(CN)_2$	54	58—59	63.63	3.54	22.62	63.83	3.57	22.67
$CH_2(CO_2C_2H_5)_2$	93	74—75	60.39	5.65	17.14	60.63	5.36	17.01
$CH_3COCH_2CO_2C_2H_5$[a)]	64	122—124[a)]	54.82	4.33	12.22	54.75	4.21	12.16

a) This compound was isolated as its 2,4-dinitrophenyl hydrazone.

were recovered quantitatively. However, the reaction of 2 moles of *N*-phenylthiopyrrolidine and 1 mol of cyclohexanone in methylene chloride at room temperature for 20 hr, followed by acid hydrolysis gave 2,6-bis(phenylthio)cyclohexanone in 67% yield.

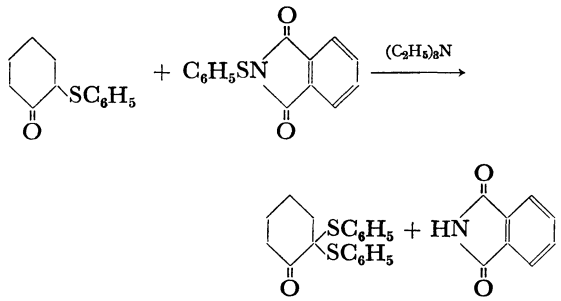


A convenient method for the preparation of α-mono-sulfenylated ketones was established by the reactions of *N*-phenylthiophthalimide with enamines. For example, the reaction of 1-piperidinocyclohexene with *N*-phenylthiophthalimide in tetrahydrofuran at room temperature for 4 hr, followed by acid hydrolysis, afforded 2-phenylthiocyclohexanone and phthalimide in 74% and quantitative yields, respectively.



Similarly, α-mono-sulfenylated ketones were obtained in good yields by the reactions of *N*-phenylthiophthalimide with 4-methyl-1-piperidinocyclohexene, β-piperidinostyrene, or 1-piperidino-1-butene (Table 4).

It was found that the α-*gem*-di-sulfenylated ketones were obtained by the reactions of mono-sulfenylated ketones with *N*-phenylthiophthalimide in the presence of a base. When 2-phenylthiocyclohexanone was stirred with *N*-phenylthiophthalimide and triethylamine in methylene chloride, 2,2-bis(phenylthio)cyclohexanone was obtained in 55% yield.



It was found that *N*-phenylthiobenzamidine hydrochloride could be isolated as a white stable solid by the reaction of *N*-phenylthiobenzamidine with hydrochloric acid in benzene. No report has been found on the isolation of hydrochloride of the sulfenamide because of the facile cleavage of the sulfur-nitrogen bond by the action of hydrochloric acid to afford sulfenyl chloride and amine hydrochloride.

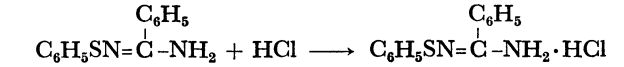
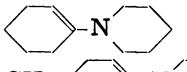
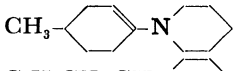
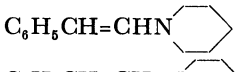
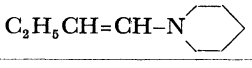
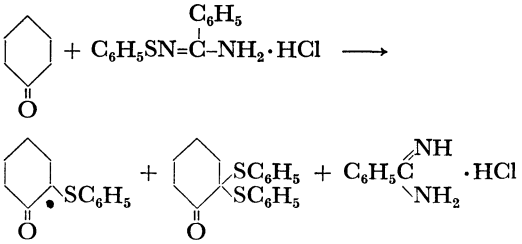


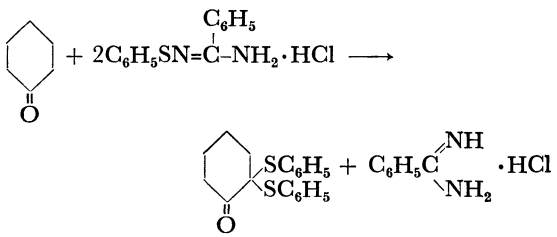
Table 4. Reactions of enamines with *N*-phenylthiophthalimide

Enamine	α-Mono-sulfenylated ketone	
	Yield (%)	Bp °C/mmHg
	74	122—124/2
	75	127—131/2
	65	135—138/2
	50	98—100/2

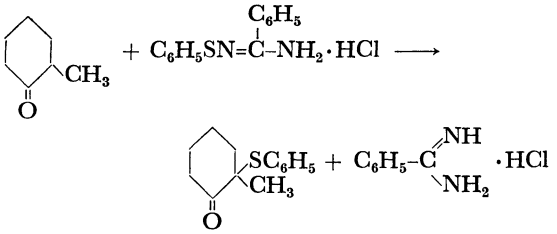
It was found that *N*-phenylthiobenzamidine hydrochloride reacted with ketones to afford α-mono-sulfenylated ketones in fairly good yields. For example, the equimolar reaction of *N*-phenylthiobenzamidine hydrochloride with cyclohexanone in dimethyl sulfoxide at room temperature resulted in the formation of 2-phenylthiocyclohexanone and 2,2-bis(phenylthio)cyclohexanone in 40% and 15% yields, respectively.



In the case of the reaction of 2 moles of *N*-phenylthiobenzamidine hydrochloride with 1 mol of cyclohexanone in dimethyl sulfoxide at room temperature, 2,2-bis(phenylthio)cyclohexanone was obtained in 70% yield.

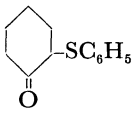
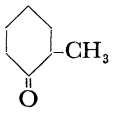
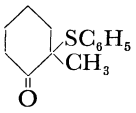
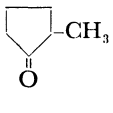
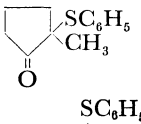
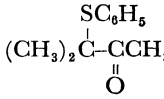
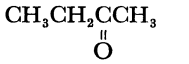
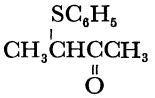


Sulfenylation of unsymmetric ketones by the use of the above mentioned hydrochloride was examined. When 2-methylcyclohexanone was allowed to react with *N*-phenylthiobenzamidine hydrochloride in dimethyl sulfoxide at room temperature, 2-methyl-2-phenylthiocyclohexanone was exclusively obtained in 57% yield.



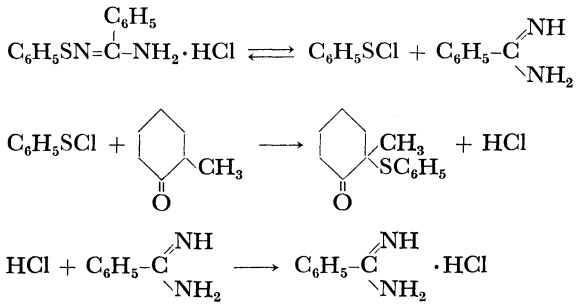
2-Methyl-2-phenylthiocyclopentanone, 2-methyl-2-phenylthio-3-butanone or 3-phenylthio-2-butanone was obtained by the reaction of *N*-phenylthiobenzamidine hydrochloride with 2-methylcyclopentanone, 2-methyl-

Table 5. Reactions of *N*-phenylthiobenzamidine hydrochloride with ketones

Ketone	Structure	Product Yield (%)	Product NMR (τ)	Anal. of 2,4-dinitrophenylhydrazone Found (Calcd) C	H	N	S
		40	—		—		
		57	8.88(S 3H) 7.6—8.5(M 8H) 2.75(S 5H)	56.98 (56.99	4.85 5.04	13.89 13.99	7.69 7.89)
		58	8.80(S 3H) 7.3—8.3(M 6H) 2.70(M 5H)	55.32 (55.95	4.69 4.70	14.80 14.50	8.21 8.29)
		44	8.65(S 6H) 7.70(S 3H) 2.85(S 5H)	54.71 (54.54	4.91 4.86	15.25 14.97	8.39 8.56)
		30	8.55(D 3H) 7.75(S 3H) 6.30(Q 1H)2.70(M 5H)	53.60 (53.33	4.46 4.48	16.10 15.55)	

3-butanone or 2-butanone, respectively (Table 5). The results show that sulfenylation of unsymmetric-ketones by the use of *N*-phenylthiobenzamidine hydrochloride occurs on the α-carbon of ketones bearing the larger number of alkyl groups.

The reactions could be interpreted as follows.



At first, an active intermediate, benzenesulfenyl chloride, is generated from *N*-phenylthiobenzamidine hydrochloride in dimethyl sulfoxide along with benzamidine. The chloride in turn reacts with ketones to afford α-sulfenylated ketones and hydrogen chloride. The benzamidine acts as a hydrogen chloride scavenger. The presence of benzenesulfenyl chloride can be supposed from the following. (1) Sulfenylation of unsymmetric-ketone with the use of *o*-nitrobenzenesulfenyl chloride occurs on the α-carbon of ketone bearing larger number of alkyl groups.[3] (2) The reaction of cyclohexene with *N*-phenylthiobenzamidine hydrochloride in dimethyl sulfoxide affords 2-chlorocyclohexyl phenyl sulfide. The same compound was also obtained by the reaction of cyclohexene with benzenesulfenyl chloride in methylene chloride.[4]

It should be noted that the reactions of active methylene compounds with sulfenamides derived from secondary amines afforded mono-sulfenylated compounds. The reactions of active methylene compounds with sulfenamides derived from imides gave di-sulfenylated compounds.

Mono-sulfenylated ketones are prepared by the reactions of enamines with sulfenamides derived from imide or the reactions of *N*-phenylthiobenzamidine hydrochloride with ketones. *gem*-Di-sulfenylated ketones are prepared by the reactions of α-mono-sulfenylated ketones with sulfenamides derived from imides in the presence of a base.

Experimental

Reaction of N,N-*Diethylbenzenesulfenamide with Malononitrile.* A mixture of *N,N*-diethylbenzenesulfenamide (1.81 g, 0.01 mol) and malononitrile (0.66 g, 0.01 mol) was stirred in methylene chloride (30 m*l*) at room temperature for 5 hr. Removal of the solvent under reduced pressure gave white crystals. Recrystallization from benzene afforded diethylammonium salt of phenylthiomalononitrile 1.36 g 55% mp 85—87°C. Found: C, 62.84; H, 6.87; N, 17.14; S, 12.99%. Calcd for $C_{13}H_{17}N_3S$: C, 63.14; H, 6.93; N, 16.99; S, 12.94%. The salt was stirred in a mixture of 10% hydrochloric acid (30 m*l*) and benzene (30 m*l*) at room temperature. After stirring for 1 hr, the benzene layer was separated. Removal of the solvent gave phenylthiomalononitrile. It was recrystallized from isopropyl alcohol. (0.93 g, guantitative) mp 84—87°C. Found: C, 62.37; H, 3.37; S, 18.67%. Calcd for $C_9H_6N_2S$: C, 62.07; H, 3.47; S, 18.37%.

The reaction of *N,N*-diethylbenzenesulfenamide with dibenzoylmethane was carried out by a similar procedure. In the case of the reaction of *N,N*-diethylbenzenesulfenamide with acetylacetone, ethyl acetoacetate or ethyl malonate, the reaction was carried out without isolation of the intermediates, salts or enamines (Table 1).

3) J. A. Barltrop and K. J. Morgan, *J. Chem. Soc.*, **1960**, 4486.
4) N. Kharasch, "Organic Sulfur Compounds" Pergamon Press, New York, Vol. I, Chapter 32.

Reaction of N-*Phenylthiosuccinimide with Dibenzoylmethane in the Presence of Triethylamine.* A mixture of *N*-Phenylthiosuccinimide (2.09 g, 0.01 mol), dibenzoylmethane (1.14 g, 0.005 mol) and triethylamine (1.11 g, 0.011 mol) was stirred in methylene chloride (40 m*l*) at room temperature. After stirring was continued overnight, the solvent was removed under reduced pressure. Fifty m*l* of water was added to the residue and the resulting oil was extracted with benzene. Removal of the solvent gave a white solid. It was recrystallized from ethanol to give bis(phenylthio)dibenzoylmethane. 1.08 g (50%). Mp 184.5—185.5°C. Found: C, 73.41; H, 4.87; S, 14.39%. Calcd for $C_{27}H_{20}O_2S_2$: C, 73.63; H, 4.58; S, 14.53%.

By a similar procedure, 3,3-bis(phenylthio)-2,3-pentanedione, bis(phenylthio)malononitrile, ethyl α,α'-bis(phenylthio) acetoacetate and ethyl bis(phenylthio)malonate were obtained by the reactions of *N*-phenylthiosuccinimide with acetylacetone, malononitrile, ethyl acetoacetate and ethyl malonate, respectively, in the presence of triethylamine (Table 3).

Reaction of N-*Phenylthiopyrrolidine with Cyclohexanone.* A mixture of *N*-phenylthiopyrrolidine (3.67 g, 0.02 mol) and cyclohexanone (1.00 g, 0.01 mol) was stirred in methylene chloride at room temperature for 20 hr. Removal of the solvent gave an oily residue. Into the residue, a mixture of 10% hydrochloric aicd (30 m*l*) and benzene (30 m*l*) was added under stirring. After stirring for 1 hr, the benzene layer was separated from the mixture and dried with sodium sulfate. The solvent was removed under reduced pressure to give an oily product. It was chromatographed on silica gel. 2,6-Bis(phenylthio)cyclohexanone was obtained from the eluate with a mixture of benzene and petroleum ether (1: 1) 1.96 g, 67%, and was confirmed by conversion into 2,4-dinitrophenylhydrazone. Mp 197—198°C. Found: C, 58.05; H, 4.51; N, 11.50; S, 13.15%. Calcd for $C_{24}H_{22}N_4O_4S_2$: C, 58.30; H, 4.48; N, 11.33; S, 12.95%.

Reaction of 1-Piperidinocyclohexene with N-*Phenylthiophthalimide.* To a suspension of *N*-phenylthiophthalimide (2.55 g, 0.01 mol) in tetrahydrofuran (20 m*l*), a solution of 1-piperidinocyclohexene (1.67 g, 0.01 mol) in tetrahydrofuran (10 m*l*) was added dropwise. With the addition, the precipitate of *N*-phenylthiophthalimide disappeared. After stirring for 4 hr at room temperature, the solvent was removed under reduced pressure. The resulting white solid was added to 10% hydrochloric acid (20 m*l*) under stirring. After stirring for 1 hr, the reaction mixture was extracted with benzene. Removal of the solvent gave an oily residue. Purification of the residue by silica gel column chromatography gave 2-phenylthiocyclohexanone. It was further purified by distillation under reduced pressure. 122—124°C/2 mmHg. 1.52 g (74%). The structure of the compound was confirmed by a direct comparison of its IR spectra with those of the authentic sample.[5]

Similarly, 4-methyl-2-phenylthiocyclohexanone, phenyl(phenylthio)acetaldehyde and 2-phenylthiobutyraldehyde were obtained by the reactions of 4-methyl-1-piperidinocyclohexene, β-piperidinostyrene and 1-piperidinobutene with *N*-phenylthiophthalimide (Table 4).

Reaction of 2-Phenylthiocyclohexanone with N-*Phenylthiophthalimide in the presence of Triethylamine.* A mixture of 2-phenylthiocyclohexanone (41.2 g, 0.2 mol), *N*-phenylthiophthalimide (51 g, 0.2 mol) and triethylamine (22 g, 0.22 mol) was refluxed in methylene chloride (300 m*l*) for 4 hr. The resulting precipitate, phthalimide, was filtered off and filtrate was evaporated under reduced pressure. One hundred m*l* of benzene was added to the residue and the resulting phthalimide was filtered again. Removal of the solvent under reduced pressure gave crystalline solids. Recrystallization from ethanol afforded 2,2-bis(phenylthio)cyclohexanone 36.09 g, 55%, mp 120—122°C. Found: C, 68.77; H, 5.97; S, 20.32%. Calcd for $C_{18}H_{18}OS_2$: C, 68.78; H, 5.77; S, 20.36%.

Preparation of N-*Phenylthiobenzamidine Hydrochloride.* To a solution of *N*-phenylthiobenzamidine (2.28 g, 0.01 mol) in benzene, 6N hydrochloric acid (2 m*l*) was added dropwise. After stirring for 30 min, a white precipitate, *N*-phenylthiobenzamidine hydrochloride, was deposited. The precipitate was filtered under reduced pressure and dried in a desiccator without further purification. 2.30 g, (87%), mp 120—121°C (decomp.). Found: C, 59.28; H, 4.69; N, 10.31; S, 12.12%. Calcd for $C_{13}H_{13}N_2SCl$: C, 58.98; H, 4.91; N, 10.59; S, 12.10%.

Reaction of N-*Phenylthiobenzamidine Hydrochloride with Equimolar Amounts of Cyclohexanone.* A mixture of *N*-phenylthiobenzamidine hydrochloride (1.32 g, 0.005 mol) and cyclohexanone (0.49 g, 0.005 mol) was stirred in dimethyl sulfoxide (20 m*l*) at room temperature for 6 hr. The mixture was added into 300 m*l* of water and the resulting oil was extracted with benzene. The benzene layer was evaporated under reduced pressure to give an oily residue. The residue was chromatographed on silica gel. 2-Phenylthiocyclohexanone (0.41 g, 40%) and 2,2-bis(phenylthio)cyclohexanone (0.12 g, 15%) were obtained from the eluate with a mixture of benzene and petroleum ether (1: 1).

By a similar procedure, 2-methyl-2-phenylthiocyclohexanone, 2-methyl-2-phenylthiocyclopentanone, 2-methyl-2-phenylthio-3-butanone, and 3-phenylthio-2-butanone were obtained from the reaction of *N*-phenylthiobenzamidine hydrochloride with 2-methylcyclohexanone, 2-methylcyclopentanone, 3-methyl-2-butanone and 2-butanone.

Reaction of 2 mol of N-*Phenylthiobenzamidine Hydrochloride with 1 Mol of Cyclohexanone.* A mixture of *N*-phenylthiobenzamidine hydrochloride (1.32 g, 0.005 mol) and cyclohexanone (0.25 g, 0.0025 mol) was stirred in dimethyl sulfoxide (20 m*l*) at room temperature for 6 hr. The mixture was added to 300 m*l* of water and the resulting oil was extracted with benzene. The solvent was removed under reduced pressure and residue was purified by silica gel column chromatography. From the eluate with a mixture of benzene and petroleum ether (1: 1), 2,2-bis(phenylthio)cyclohexanone was obtained, 0.55 g (70%) mp 122—123°C.

5) R. Wilputte and R. H. Martin, *Bull. Soc. Chim. Belg.*, **65**, 874 (1956); *Chem. Abst.*, **51**, 6588i.