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S-Alkylthioisothioureas. II.[1] Reactions of S-Alkylthioisothioureas with Some Active Methylene Compounds and Secondary Amines

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S-Alkylthioisothioureas were found to react with various active methylene compounds and secondary amines to give alkylthiomethylene derivatives and sulfenamides, respectively.

We have recently described the synthesis of S-alkylthioisothioureas and their reactions with various kinds of thiol compounds.[3] The fact that the reaction of S-alkylthioisothioureas with thiol compounds results in the facile formation of unsymmetrical disulfides which are generally accessible only with difficulty prompted us to explore a new alkylthiation of various compounds with S-alkylthioisothioureas. In this paper will be described the reaction of S-alkylthioisothioureas with some active methylene compounds and secondary amines.

Reactions with Active Methylene Compounds

The alkylthiation of active methylene compounds with S-alkylthioisothioureas has not been reported, although a few methods[4-6] are available for the alkylthiation of active methylene compounds with other reagents. We found that the reaction of S-alkylthioisothioureas (**1**) with acetylacetone (**2**) proceeds readily in ether to give mono-alkylthiated compounds, 3-alkylthiopentane-2,4-diones (**3**—**6**), in good yields. This reaction was extended to various kinds of **1** and active methylene compounds. Cyanoacetamide (**7**, R_3=CN) and malonodiamide (**8**, R_3=$CONH_2$) gave, on the other hand, the di-alkylthiated compounds (**9**—**12**) and the mono-alkylthiated compounds were not observed. These reactions are briefly shown in Chart 1 and the results are summarized in Tables I and II. It may be considered that the difference between the mono- and di-alkylthiations depends partly on the

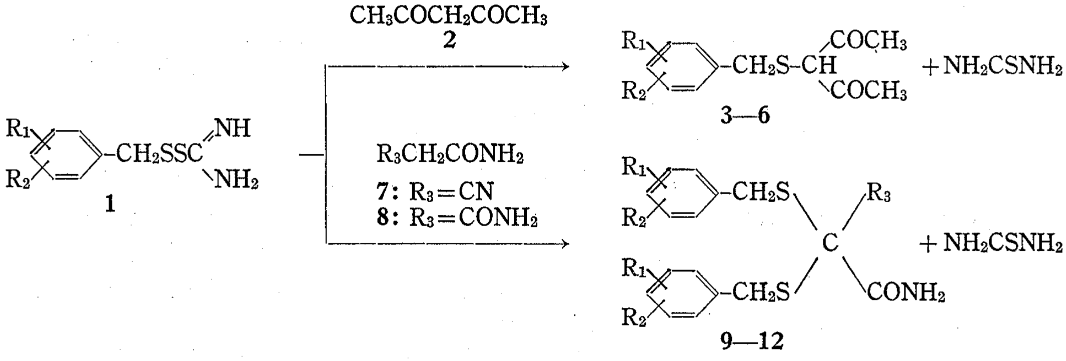

Chart 1

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[1] A part of this paper was presented at the 21st Annual Meeting of Kinki Branch, Pharmaceutical Society of Japan, Osaka, November, 1971.

[2] Location: *Juso-Nishino-cho, Higashiyodogawa-ku, Osaka.*

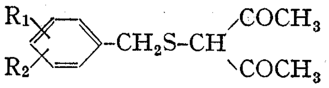
[3] K. Sirakawa, O. Aki, T. Tsujikawa and T. Tsuda, *Chem. Pharm. Bull.* (Tokyo), **18**, 235 (1970).

[4] S. Hayashi, M. Furukawa, J. Yamamoto and K. Niigata, *Chem. Pharm. Bull.* (Tokyo), **15**, 1188 (1967).

[5] T. Mukaiyama, S. Kobayashi and T. Kumamoto, *Tetrahedron Letters*, **1970**, 5115.

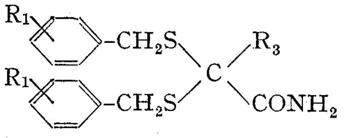
[6] H.H. Otto, *Arch. Pharm.*, 304(7), 504 (1971).

Table I. 3-Alkylthiopentane-2,4-diones



No.	R_1	R_2	mp (°C)	Yield (%)	Formula	Analysis (%) Calcd. C	Calcd. H	Calcd. S	Found C	Found H	Found S
3	H	H	50— 53	67	$C_{12}H_{14}O_2S$	64.87	6.34	14.42	64.75	6.17	14.30
4	2-Cl	H	36— 38	52	$C_{12}H_{13}O_2SCl$	55.91	5.08		56.01	4.92	
5	4-Cl	H	53— 55	62	$C_{12}H_{13}O_2SCl$	55.91	5.08	12.44	56.12	5.15	12.29
6	2-Cl	6-Cl	100—102	82	$C_{12}H_{12}O_2SCl_2$	49.44	4.15	11.01	49.26	4.01	11.48

Table II. Dialkylthiated Compounds



No.	R_1	R_3	mp (°C)	Yield (%)	Formula	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Calcd. S	Found C	Found H	Found N	Found S
9	H	CN	118—120	95	$C_{17}H_{16}ON_2S_2$	62.16	4.90	8.52	19.52	62.11	4.87	8.42	19.50
10	H	$CONH_2$	214—216	41	$C_{17}H_{18}O_2N_2S_2$	58.93	5.23	8.08	18.50	58.82	5.25	7.84	18.33
11	2-Cl	CN	124—126	75	$C_{17}H_{14}ON_2S_2Cl_2$	51.38	3.55	7.05		51.47	3.37	7.11	
12	4-Cl	CN	115—117	40	$C_{17}H_{14}ON_2S_2Cl_2$	51.38	3.55	7.05		50.74	3.68	6.99	

reactivities of the active methylene compounds, but the mechanism leading to different products has not been well understood.[7]

As an extension of this facile alkylthiation some heterocyclic compounds bearing an active methylene group were investigated. Thus the reaction of **1** with 1,2-diphenylpyrazolidine-3,5-dione (**13**) and 1-phenyl-3-methylpyrazol-5-one (**14**) in aqueous ethanolic solution

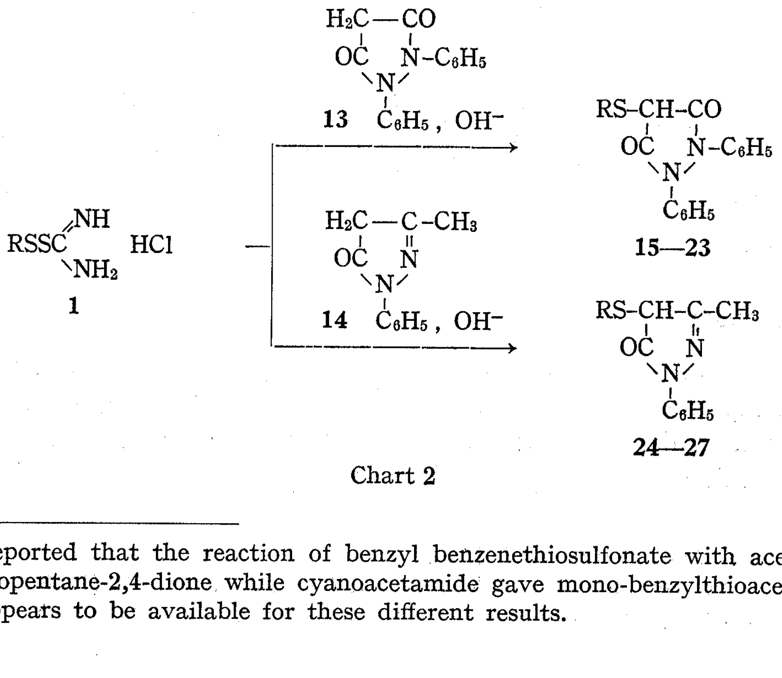


Chart 2

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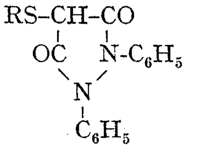
[7] It has been reported that the reaction of benzyl benzenethiosulfonate with acetylacetone afforded 3,3-dibenzylthiopentane-2,4-dione while cyanoacetamide gave mono-benzylthioacetamide.[4] No clear explanation appears to be available for these different results.

afforded 1,2-diphenyl-4-alkylthiopyrazolidine-3,5-diones (**15**—**23**) and 1-phenyl-3-methyl-4-alkylthiopyrazol-5-ones (**24**—**27**), respectively, in good yields (Chart 2), and the results are summarized in Tables III and IV.

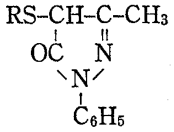
TABLE III. 1,2-Diphenyl-4-alkylthiopyrazolidine-3,5-diones



No.	R	mp (°C)	Yield (%)	Formula	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
15	$C_6H_5CH_2CH_2$	149—150	32	$C_{23}H_{20}O_2N_2S$	71.11	5.19	7.21	71.01	5.04	7.14
16	$C_6H_5CH_2$	173—175	17	$C_{22}H_{18}O_2N_2S$	70.56	4.85	7.48	70.43	4.53	7.43
17	$HOCH_2CH_2$	152	28	$C_{17}H_{16}O_3N_2S$	62.17	4.91	8.53	62.40	4.86	8.53
18	$4\text{-}CH_3O\text{-}C_6H_4CH_2$	130—133	55	$C_{23}H_{19}O_3N_2S$	68.46	4.74	6.94	68.01	5.02	6.70
19	2,6-diCl$C_6H_3CH_2$	203—205	30	$C_{22}H_{16}O_2N_2SCl_2$	59.59	3.63	6.31	59.57	3.92	6.19
20	4-Cl$C_6H_4CH_2$	159—160	52	$C_{22}H_{17}O_2N_2SCl$	64.61	4.19	6.84	64.24	4.23	6.49
21	2-Cl$C_6H_4CH_2$	133—134	58	$C_{25}H_{20}O_2N_2SCl$ a)	67.03	4.50	6.25	67.32	4.49	6.21
22	*n*-C_3H_7	290—292	57	$C_{18}H_{17}O_2N_2SNa$ b)	62.05	4.91	8.04	61.66	4.98	7.99
23	*n*-C_4H_9	270	56	$C_{19}H_{21}O_3N_2SNa$ c)	59.98	5.56	7.36	60.09	5.58	7.27

a) $C_{22}H_{17}O_2N_2SCl\ 1/2C_6H_6$ *b*) Na-Salt *c*) Na-Salt-H_2O

TABLE IV. 1-Phenyl-3-methyl-4-alkylthiopyrazol-5-ones



No.	R	mp (°C)	Yield (%)	Formula	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
24	$C_6H_5CH_2$	176—178	49	$C_{17}H_{16}ON_2S$	68.88	5.44	9.45	69.19	5.39	9.22
25	2-Cl$C_6H_4CH_2$	202—204	75	$C_{17}H_{15}ON_2SCl$	61.71	4.57	8.46	62.04	4.51	8.41
26	2-F$C_6H_4CH_2$	178—179.5	76	$C_{17}H_{15}ON_2SF$		10.20 a)	8.91		10.37 b)	8.88
27	2,6-diCl$C_6H_3CH_2$	193—194	74	$C_{17}H_{14}ON_2SCl_2$	55.89	3.86	7.66	56.00	3.96	7.41

a) S: Calcd. *b*) S: Found

Reactions with Secondary Amines

From the results of ready formation of unsymmetrical disulfides[3] and facile alkylthiation of active methylene compounds it appeared to us that **1** might react with secondary amines to give sulfenamide derivatives. The sulfenyl reagents currently available for the synthesis of sulfenamides are sulfenyl chlorides, sulfenyl thiocyanates and thiol sulfonates.[8–10]

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8) E. Riesz, *Bull. Soc. Chim. France*, **1966**, 1449.
9) N. Kharasch, S.J. Potempa and H.L. Wehrmeister, *Chem. Rev.*; **39**, 269 (1946).
10) C. Brown and B.T. Grayson, *Mechanism of Reactions of Sulfur Compounds*, **5**, 93 (1970).

The instability of these sulfenyl reagents, however, restricts their utility and no satisfactory method for the preparation of aralkyl sulfenamides has so far been found.[11]

When an excess of secondary amine such as morpholine, piperidine, N-benzylpiperazine and dibenzylamine was added to a solution of **1** in methanol at room temperature insoluble substances, aralkyl sulfenamides (**28**—**31**), separated immediately. The structural assignment of the products was made on the basis of the elemental analyses, IR and NMR spectral data; the compound **28**, for example, showed the IR absorptions at 700 and 770 cm^{-1} (monosubstituted aromatic system) and no absorption at the region of 1650 cm^{-1} (C=N stretching of isothiourea) was observed. The NMR spectrum showed benzylic methylene protons at δ 3.92 ppm as a singlet. The compounds obtained in these reactions were summarized in Table V.

Similarly, when **1** was treated with piperazine and N-phenylpiperazines, N,N'-bis-aralkylthiopiperazine and N-phenyl-N'-aralkylthiopiperazine derivatives were obtained respectively in good yields (Chart 3). The results were summarized in Tables VI and VII.

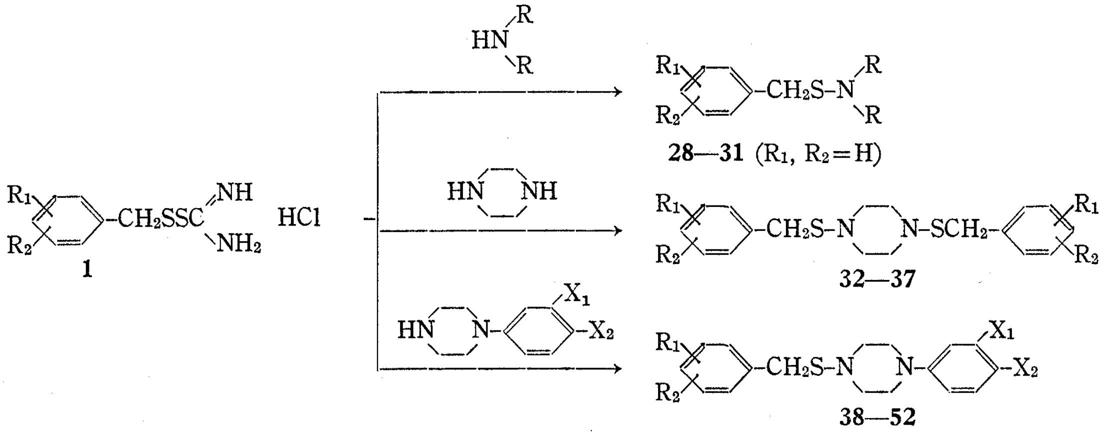
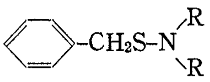
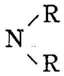
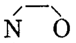
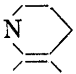
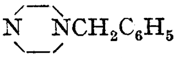


Chart 3

TABLE V. N-Benzylthioamines



No.		mp (°C)	Yield (%)	Formula	Analysis (%) Calcd. C	H	N	S	Found C	H	N	S
28		74—76	60	$C_{11}H_{15}ONS$	63.12	7.22	6.69	15.31	62.92	7.15	6.29	15.15
29		30—32	20	$C_{12}H_{17}NS$	69.51	8.26	6.75	15.48	69.54	8.16	6.63	15.24
30	 $NCH_2C_6H_5$	64—66	60	$C_{18}H_{22}N_2S$	72.43	7.43	9.38		72.57	7.50	9.34	
31	$N(CH_2C_6H_5)_2$	83—85	37	$C_{21}H_{21}NS$	78.95	6.62	4.38	10.05	78.95	6.69	4.38	10.11

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[11] One simple aralkyl sulfenamide was synthesized[12,13] by means of benzyl benzenethiosulfonate but this procedure is accompanied, as pointed out,[14] by the amine salt of the sulfinic acid which is difficult to be separated from the desired compound.

[12] J.E. Dunbar and J.H. Rogers, *J. Org. Chem.*, **31**, 2842 (1966).

[13] S. Hayashi, M. Furukawa, Y. Fujino and H. Matsukura, *Chem. Pharm. Bull.* (Tokyo), **17**, 954 (1969).

[14] N.E. Heimer and L. Field, *J. Org. Chem.*, **35**, 3012 (1970).

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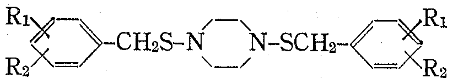
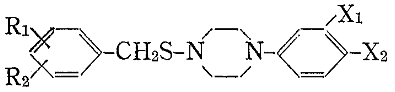
Table VI. N,N′-Bis-benzylthiopiperazines



No.	R_1	R_2	mp (°C)	Yield (%)	Formula	Analysis (%)							
						Calcd.				Found			
						C	H	N	S	C	H	N	S
32	H	H	149—150	35	$C_{18}H_{22}N_2S_2$	65.41	6.70	8.49	19.40	65.44	6.52	8.23	18.07
33	2-Cl	H	134—136	43	$C_{18}H_{20}N_2S_2Cl_2$	54.12	5.04	7.01	16.05	54.10	5.01	6.88	15.52
34	4-Cl	H	157—158	49	$C_{18}H_{20}N_2S_2Cl_2$	54.12	5.04	7.01	16.05	54.59	4.97	6.94	15.91
35	2-Cl	6-Cl	140—141	61	$C_{18}H_{18}N_2S_2Cl_4$	46.17	3.86	5.94	13.64	45.64	3.74	5.74	14.32
36	4-$(CH_3)_2CH$	H	133—135	70	$C_{24}H_{34}N_2S_2$	69.99	8.26		15.45	69.57	8.34		15.33
37	4-$(CH_3)_3C$	H	172—173	57	$C_{26}H_{38}N_2S_2$	70.53	8.65		15.48	70.47	8.47		14.54

Table VII. N-Benzylthio-N′-phenylpiperazines



No.	R_1	R_2	X_1	X_2	mp (°C)	Yield (%)	Formula	Analysis (%)							
								Calcd.				Found			
								C	H	N	S	C	H	N	S
38	H	H	H	H	100—100.5	33	$C_{17}H_{20}N_2S$	71.79	7.08	9.85	11.28	71.82	6.97	9.74	11.13
39	H	H	H	Cl	100—100.5	27	$C_{17}H_{19}N_2SCl$	64.03	6.06	8.78		64.32	5.75	8.53	
40	H	H	Cl	H	85—87	61	$C_{17}H_{19}N_2SCl$	64.03	6.06	8.78	10.05	64.25	6.01	8.65	10.11
41	H	H	Cl	Cl	124—125	77	$C_{17}H_{18}N_2SCl_2$	57.79	5.13	7.92	9.07	58.04	5.20	7.87	9.00
42	2-Cl	H	H	Cl	60	35	$C_{17}H_{18}N_2SCl_2$	57.79	5.13	7.92	9.07	57.30	5.29	7.56	9.65
43	3-Cl	H	H	Cl	105	55	$C_{17}H_{18}N_2SCl_2$	57.79	5.13	7.92	9.07	58.04	5.12	8.01	8.91
44	4-Cl	H	H	Cl	132	11	$C_{17}H_{18}N_2SCl_2$	57.79	5.13	7.92		58.18	5.22	7.97	
45	3-Cl	H	Cl	Cl	110—111.5	73	$C_{17}H_{17}N_2SCl_3$	52.65	4.41	7.22		52.87	4.33	7.15	
46	4-Cl	H	Cl	Cl	115—118	57	$C_{17}H_{17}N_2SCl_3$	52.65	4.41			53.10	4.54		
47	2-F	H	H	Cl	75	24	$C_{17}H_{18}N_2SClF$	60.81	5.39	8.33	9.55	60.81	5.55	8.31	9.67
48	2-F	H	Cl	Cl	85—87	73	$C_{17}H_{17}N_2SCl_2F$			7.54	8.63			7.41	8.87
49	2-Cl	6-Cl	Cl	Cl	97—98	54	$C_{17}H_{16}N_2SCl_4$	48.35	3.81	6.63	7.59	48.18	3.71	6.34	8.21
50	4-CH_3O	H	H	Cl	113—114	58	$C_{18}H_{21}ON_2SCl$	61.96	6.07	8.02	9.18	62.07	6.09	8.00	9.12
51	4-$(CH_3)_3C$	H	H	Cl	160—161	80	$C_{21}H_{27}N_2SCl$	67.26	7.25	7.47		67.25	7.18	7.13	

In the previous paper$^{3)}$ we reported that the reaction of **1** with dimethylamine gave symmetrical arakyl trisulfides. In this case thiourea and dicyandiamide (**54**) were isolated as by-products, while in the sulfenamide formation described above only thiourea was isolated. The reaction of **1** with dimethylamine to yield symmetrical trisulfides would be reasonably accounted for by the mechanism which is depicted by the scheme in Chart 4. Aralkyldithio anion (**53**) which is initially formed by the reaction of **1** with dimethylamine attacks the starting material (**1**) to form symmetrical trisulfide. Cyanamide formed in this reaction was isolated as its dimer, dicyandiamide (**54**), which was proved to be identical with an authentic sample by the comparison of the IR spectrum. However the reaction of **1** with morpholine, piperidine and piperazines afforded only aralkyl sulfenamides and no trisulfides formation was observed. At present we have no definite explanation to account for these different results.

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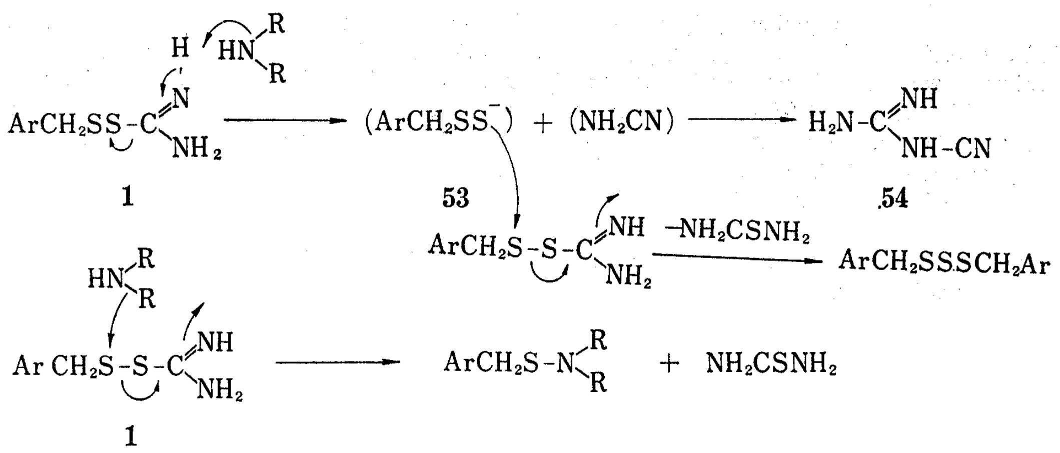

Chart 4

Experimental

All melting points are uncorrected. IR spectra were obtained with a Hitachi-215 Spectrophotometer and NMR spectra with a Varian A-60 spectrometer using TMS as internal standard.

3-Benzylthiopentane-2,4-dione (3)——a) A saturated aqueous solution of $NaHCO_3$ was added to a solution of S-benzylthioisothiourea hydrochloride (**1a**; 5.0 g) in H_2O (50 ml) and the separated oil was extracted with ether (20 ml × 2) and dried over $MgSO_4$. To this ethereal solution was added acetylacetone (2.1 g), and the mixture was heated under reflux for several minutes. The precipitated thiourea was filtered off. The filtrate was evaporated and the residual oil was kept for several hours under cooling for crystallization. Recrystallization from aqueous MeOH gave 3-benzylthiopentane-2,4-dione, mp 50—53° (Lit., mp 54—56°[4]). NMR (in $CDCl_3$); δ 2.45 (s, $2CH_3$), 3.82 (s, CH_2) and 7.28 ppm (s, aromatic).

b) A solution of **1a** (23.4 g) and acetylacetone (10.0 g) in 75% EtOH (100 ml) was treated with 5% $NaHCO_3$ solution (150 ml), and the reaction mixture was heated under reflux for 5 min. The mixture was kept overnight in a refrigerator, the precipitates were collected and recrystallized to give **3** (21.0 g), identified with the specimen obtained by the procedure a) by the mixed melting point measurement. Other mono-benzylthiated compounds obtained by similar procedures are summarized in Table I.

Bis-benzylthio-malonodiamide (10)——A solution of malonodiamide (3.0 g) and **1a** (2.3 g) in 75% EtOH (50 ml) was treated with 5% $NaHCO_3$ solution (15 ml), and the mixture was heated under reflux for 10 min. The solution was kept overnight in a refrigerator, the separated precipitates were collected and recrystallized from EtOH to give bis-benzylthio-malonodiamide, mp 214—216° (decomp.). Other dibenzylthiated compounds obtained by a similar procedure are summarized in Table II.

1,2-Diphenyl-4-(2,6-dichlorobenzylthio)pyrazolidine-3,5-dione (19)——A solution of 2,6-dichlorobenzylthioisothiourea hydrochloride (4.5 g) and 1,2-diphenyl-pyrazolidine-3,5-dione (3.9 g) in EtOH (100 ml) was treated with a solution of K_2CO_3 (2.1 g) in H_2O (20 ml), and the mixture was heated under reflux for 30 min. After cooling the precipitates were collected. Recrystallization from aqueous EtOH gave potassium salt of 1,2-diphenyl-4-(2,6-dichlorobenzylthio)pyrazolidine-3,5-dione, mp 270—272° (decomp.), in 50% yield. *Anal.* Calcd. for $C_{22}H_{15}O_2N_2SCl_2K$: C, 54.88; H, 3.14; N, 5.81. Found: C, 54.78; H, 3.12; N, 5.76. Acidification of the aqueous solution of the salt gave 1,2-diphenyl-4-(2,6-dichlorobenzylthio)pyrazolidine-3,5-dione, mp 203—205°. Compounds obtained by a similar procedure are summarized in Table III.

1-Phenyl-3-methyl-4-benzylthiopyrazol-5-one (24)——A solution of 1-phenyl-3-methyl-pyrazol-5-one (0.5 g) and **1a** (0.65 g) in 80% EtOH (20 ml) was treated with powdered $NaHCO_3$ until the pH of the solution reached 8.0. The reaction mixture was heated under reflux for 5 min, and left for several hours in a refrigerator. The precipitates were collected and recrystallized from aqueous MeOH to give 1-phenyl-3-methyl-4-benzylthiopyrazol-5-one, mp 176—178°. NMR (in $CDCl_3$); δ 2.17 (s, CH_3), 3.85 (s, CH_2) and 7.00—7.80 ppm (m, aromatic). Compounds obtained by a similar procedure are summarized in Table IV.

N-Benzylthio-morpholine (28)——To a solution of morpholine (3.8 g) in H_2O (10 ml) was added a solution of **1a** (5.0 g) in 20% MeOH (60 ml). The mixture was stirred for 30 min under ice-cooling. The crystalline precipitates were collected and recrystallized from MeOH to give N-benzylthio-morpholine, mp 74—76° (Lit.,[12] mp 74—76°). NMR (in $CDCl_3$); δ 2.92 and 3.60 (m, morpholine), 3.92 (s, CH_2) and 7.30 ppm (s, aromatic).

Bis-(4-isopropylbenzylthio)piperazine (36)——To a solution of piperazine $6H_2O$ (2.5 g) in MeOH (10 ml) was added a solution of S-4-isopropylbenzylthioisothiourea hydrochloride (1.4 g) in MeOH (10 ml). The mixture was stirred for several minutes at room temperature. The separated solid was collected and recrystallized from EtOH to give bis-(4-isopropylbenzylthio)piperazine, mp 133—135°. NMR (in $CDCl_3$); δ 1.16 and 1.27 (s, gem-CH_3), 2.80 (m, CH), 3.10 (s, piperazine), 3.95 (s, CH_2) and 7.23 ppm (s, aromatic).

N-Benzylthio-N′-(2-methylphenyl)piperazine (52)——To a solution of **1a** (2.34 g) in 30% MeOH (50 ml) was added a solution of N-(2-methylphenyl)piperazine (3.50 g) in MeOH (20 ml) under ice-cooling. The reaction mixture was stirred for 30 min, the precipitates were collected and recrystallized from aqueous MeOH to give N-benzylthio-N′-(2-methylphenyl)piperazine (2.2 g, 74.0%), mp 56—58°. NMR (in $CDCl_3$); δ 2.27 (s, CH_3), 2.80—3.25 (m, piperazine), 3.98 (s, CH_2), and 6.90—7.50 ppm (m, aromatic). *Anal.* Calcd. for $C_{18}H_{22}N_2S$: C, 72.43; H, 7.43; N, 9.38. Found: C, 72.19; H, 7.25; N, 8.90. Other sulfenamides obtained by a similar procedure are summarized in Tables V, VI, and VII.

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