

3-Alkylthio and 3-Aminopyrazolo[3,4-*d*]pyridazines. Ring Contraction of Pyridazino[4,5-*e*][1,3,4]thiadiazines *via* Extrusion of Sulfur

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Reaction of 4-chloro-2-methyl-5-(1-methylhydrazino)-3(2*H*)-pyridazinone (**1**) with carbon disulfide followed by alkylation yielded 2-alkylthio-4*H*-pyridazino[4,5-*e*][1,3,4]thiadiazine derivatives **2**. Oxidative cyclization of 5-(4-substituted 1-methylthiosemicarbazido)-3(2*H*)-pyridazinone derivatives **4** with *N*-bromosuccinimide also gave 2-substituted amino-4*H*-pyridazino[4,5-*e*][1,3,4]thiadiazine derivatives **5**. Heating of **2** and **5** resulted in ring contraction to afford the corresponding pyrazolo[3,4-*d*]pyridazine derivatives **6**, **7** *via* sulfur extrusion. A possible mechanism for the desulfurization reaction is discussed, comparing with a structural difference between a type of pyridazino[4,5-*e*][1,3,4]thiadiazine (**2**, **5**) and another one (**9**, **11**, **13**, **15**).

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The chemistry of 1,3,4-benzothiadiazines [1-4] has been developed by several groups of investigators with a number of attractive approaches. In recent years, attention has been gradually paid to the synthesis of 1,3,4-thiadiazines condensed with heterocycles such as pyridine [5], pyrimidine [5,6], 1,2,4-triazine [7], quinoxaline [5,8] and indole [9], among which are also found interestingly an inhibitor of cyclic nucleotide phosphodiesterase [6] and a dyestuff [8].

Recent papers from our laboratory [10] have dealt with the synthesis of 7-substituted 2-phenyl-4*H*-pyridazino[4,5-*e*][1,3,4]thiadiazin-8(7*H*)-ones and their conversion into 5-substituted 3-phenyl-1*H*-pyrazolo[3,4-*d*]pyridazin-4(5*H*)-ones by ring contraction through sulfur extrusion, among which have been found some derivatives with selective herbicidal activities [11].

We would like here to describe the synthesis of some

Scheme 1

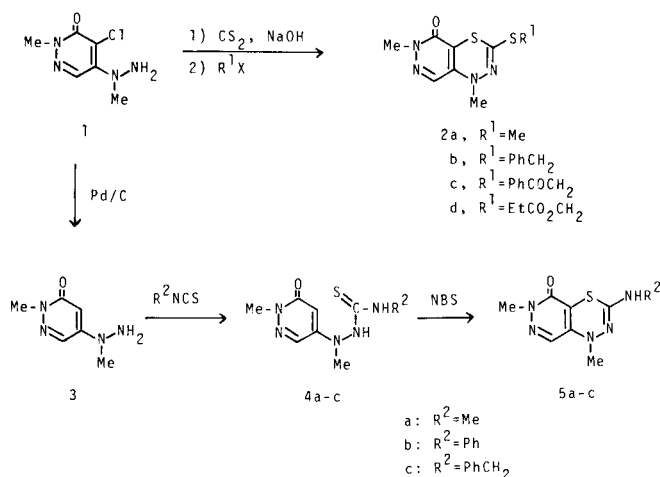


Table I

Physical and Analytical Data for Compounds **2a-d** and **5a-c**

Compound	Appearance	Mp (°C)	Yield (%)	Molecular Formula	Analysis % Calcd./Found		
					C	H	N
2a	orange needles	144-145	70	C ₈ H ₁₀ N ₄ OS ₂	39.65	4.16	23.12
					39.49	4.21	23.24
2b	red needles	125-126	75	C ₁₄ H ₁₄ N ₄ OS ₂	52.81	4.43	17.60
					52.96	4.47	17.71
2c	orange needles	181-182	68	C ₁₅ H ₁₄ N ₄ O ₂ S ₂	52.01	4.07	16.17
					52.27	3.96	16.31
2d	red needles	66-67	59	C ₁₁ H ₁₄ N ₄ O ₃ S ₂	42.03	4.49	17.82
					41.94	4.52	17.99
5a	red needles	200-202	63	C ₈ H ₁₁ N ₅ OS	42.65	4.92	31.09
					42.73	4.78	31.04
5b	red needles	207-209	68	C ₁₃ H ₁₃ N ₅ OS	54.34	4.56	24.37
					54.49	4.44	24.30
5c	red needles	156-158	71	C ₁₄ H ₁₅ N ₅ OS	55.80	5.02	23.24
					55.52	4.90	23.27

pyridazino[4,5-*e*][1,3,4]thiadiazines possessing alkylthio and alkyl or arylamino substituents at the 2-position and their competence of the ring transformation into the corresponding pyrazolo[3,4-*d*]pyridazine derivatives, through desulfurization under thermal condition.

4-Chloro-2-methyl-5-(1-methylhydrazino)-3(2*H*)-pyridazinone (**1**) [12] was reacted with carbon disulfide in the presence of sodium hydroxide in dimethylformamide at room temperature, followed by alkylation with methyl iodide, to give 4,7-dimethyl-2-methylthio-4*H*-pyridazino[4,5-*e*][1,3,4]thiadiazin-8(7*H*)-one (**2a**) in 53% yield. The assigned structure for **2a** was confirmed by its elemental analysis ($C_{18}H_{10}N_4OS$), mass spectrum (m/e 242, M^+) and proton nuclear magnetic resonance (1H -nmr) spectrum, in which two *N*-methyl groups and an *S*-methyl groups were observed. Similarly, reaction of compound **1** with carbon disulfide followed by alkylation with benzyl bromide, phenacyl bromide and ethyl chloroacetate gave the corresponding 2-alkylthio-4,7-dimethyl-4*H*-pyridazino[4,5-*e*][1,3,4]thiadiazine derivatives **2b-d** in respective yields of 57%, 65% and 37%.

2-Methyl-5-(1-methylhydrazino)-3(2*H*)-pyridazinone (**3**), obtained by catalytic hydrogenolysis of compound **1**, was reacted with alkyl or aryl isothiocyanate in dimethylformamide to afford the corresponding 2-methyl-5-(4-substituted 1-methylthiosemicarbazido)-3(2*H*)-pyridazinones **4a-c** in good yield. Oxidation of **4a** with *N*-bromosuccinimide [6] in chloroform at room temperature gave the cyclized

product 4,7-dimethyl-2-methylamino-4*H*-pyridazino[4,5-*e*][1,3,4]thiadiazin-8(7*H*)-one (**5a**) in 48% yield. The assigned structure for **5a** was established by its elemental analysis ($C_{18}H_{11}N_5OS$), mass spectrum (m/e 225, M^+) and proton nuclear magnetic resonance spectrum, in which three *N*-methyl groups were observed and a signal due to the proton at the 4-position of **4a** was lost. Similar treatment of **4b, c** with *N*-bromosuccinimide yielded the corresponding pyridazino[4,5-*e*][1,3,4]thiadiazine derivatives **5b, c** in 68% and 56% yields, respectively.

Reaction of compound **1** with benzyl isothiocyanate similarly afforded 5-(4-benzyl-1-methylthiosemicarbazido)-4-chloro-2-methyl-3(2*H*)-pyridazinone (**4'c**) in 76% yield. However, an attempted cyclization of **4'c** to **5c**, in basic media, was unsuccessful. Some results from reaction of **4'c** with triethylamine or sodium hydroxide in dimethylformamide under several conditions are shown in Table III. Scarcely any cyclization was observed at room temperature only to recover the starting material. Under refluxing conditions **4'c** gave 3-benzylamino-1,5-dimethyl-1*H*-pyrazolo[3,4-*d*]pyridazin-4(5*H*)-one (**7c**) as the sole product, formed by desulfurization of the cyclized intermediate **5c** during the course of reaction. The desulfurization reaction will be mentioned later in detail again. Heating of **4'c** with sodium hydroxide at 50° for 14 hours afforded a mixture of pyridazino[4,5-*e*][1,3,4]thiadiazine derivative **5c** and pyrazolo[3,4-*d*]pyridazine derivative **7c** in the ratio of *ca.* 3:2 together with starting material (41% yield recovery). Similarly, heating of **4'c** at 80° for 3 hours gave compounds **5c** and **7c** in the ratio of *ca.* 2:1 together with a small amount of starting material. Alternative reaction conditions (base, solvent, temperature and time) for the cyclization were attempted, to prove difficult to set up a crucial condition yielding **5c** favorably, without contamination of **7c**.

Table II

Spectral Data for Compounds **2a-d** and **5a-c**

Compound	IR ν cm^{-1} (potassium bromide)	1H -NMR [a] δ
2a	1620 (CO)	2.95 (3H, s, SCH_3), 3.33 (3H, s, NCH_3), 3.70 (3H, s, NCH_3), 7.47 (1H, s, H-5)
2b	1615 (CO)	3.35 (3H, s, NCH_3), 3.75 (3H, s, NCH_3), 4.24 (2H, s, SCH_2), 7.32 (5H, s, C_6H_5), 7.46 (1H, s, H-5)
2c	1625 (CO) 1670 (CO)	3.19 (3H, s, NCH_3), 3.73 (3H, s, NCH_3), 4.51 (2H, s, SCH_2), 7.43 (1H, s, H-5), 7.46-8.10 (5H, m, C_6H_5)
2d	1620 (CO) 1730 (CO)	1.25 (3H, t, $J = 7$ Hz, CH_2CH_3), 3.29 (3H, s, NCH_3), 3.70 (3H, s, NCH_3), 3.75 (2H, s, SCH_2), 4.17 (2H, q, $J = 7$ Hz, OCH_2CH_3), 7.42 (1H, s, H-5)
5a	1620 (CO) 3240 (NH)	2.75 (3H, s, NCH_3), 3.22 (3H, s, NCH_3), 3.61 (3H, s, NCH_3), 6.54 (1H, br, NH), 7.65 (1H, s, H-5)
5b	1630 (CO) 3240 (NH)	3.34 (3H, s, NCH_3), 3.63 (3H, s, NCH_3), 6.81-7.65 (5H, m, C_6H_5), 7.78 (1H, s, H-5), 9.10 (1H, br, NH)
5c	1610 (CO) 3270 (NH)	3.23 (3H, s, NCH_3), 3.61 (3H, s, NCH_3), 4.40 (2H, d, $J = 6$ Hz, NCH_2), 4.95 (1H, br, NH), 7.38 (5H, s, C_6H_5), 7.45 (1H, s, H-5)

[a] All compounds were measured in deuteriochloroform except **5a, 5b** (in dimethylsulfoxide- d_6).

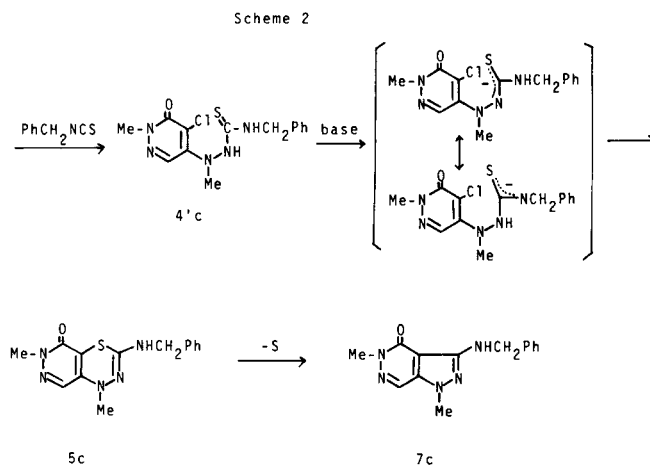


Table III
Reaction of 4'c with Base

Run	Solvent	Base	Temperature	Time	Result
1	Dimethylformamide	Triethylamine	room temperature	12	4'c (recovery)
2	Dimethylformamide	Triethylamine	100°	3	4'c (recovery)
3	Dimethylformamide	Triethylamine	reflux	3	7c (64%)
4	Dimethylformamide	Sodium Hydroxide	room temperature	12	4'c (recovery)
5	Dimethylformamide	Sodium Hydroxide	50°	14	5c (29%) + 7c (21%) + 4'c (41%)
6	Dimethylformamide	Sodium Hydroxide	80°	3	5c (53%) + 7c (25%) + 4'c (8%)
7	Dimethylformamide	Sodium Hydroxide	reflux	3	7c (70%)

4,5-Dichloro-5-(1-methylhydrazino)pyridazine (**8**) was reacted with carbon disulfide followed by methylation, similarly as in compound **1**, to give 8-chloro-4-methyl-2-methylthio-4*H*-pyridazino[4,5-*e*][1,3,4]thiadiazine (**9**) in 44% yield. 5-(4-Benzyl-1-methylthiosemicarbazido)-4,5-dichloropyridazine (**10**), prepared from compound **8** with benzyl isothiocyanate, was heated in dimethylformamide in the presence of sodium hydroxide to afford 2-benzylamino-8-chloro-4-methyl-4*H*-pyridazino[4,5-*e*][1,3,4]thiadiazine (**11**) in 39% yield. 4,7-Dimethyl-2-methylthio-4*H*-pyridazino[5,6-*e*][1,3,4]thiadiazin-6(7*H*)-one (**13**) (39% yield) and 2-benzylamino-4,7-dimethyl-4*H*-pyridazino[5,6-*e*][1,3,4]thiadiazin-6(7*H*)-one (**15**) (44% yield) were also obtained likewise from 6-chloro-2-methyl-5-(1-methylhydrazino)-3(2*H*)-pyridazinone (**12**) and 5-(4-benzyl-1-methylthiosemicarbazido)-6-chloro-2-methyl-3(2*H*)-pyridazinone (**14**), derived from compound **12** with benzyl isothiocyanate, respectively.

Compound **2a** was heated in boiling toluene, while the color of the reaction mixture changed from orange to pale yellow, and heating was continued for 12 hours to complete the reaction. Appropriate work-up of the resulting mixture afforded the ring contracted product, through extrusion of sulfur, 1,5-dimethyl-3-methylthio-1*H*-pyrazolo[3,4-*d*]pyridazin-4(5*H*)-one (**6a**) in 68% yield. The assigned structure for **6a** was confirmed by the spectral and elemental analysis data. The desulfurization of **2a** also proceeded in a boiling dimethylformamide solution so rapidly as it reached termination within 1 hour to give **6a** in the same yield as in toluene. Similarly, alternative 2-alkylthiopyridazino[4,5-*e*]thiadiazine derivatives **2b-d**, by heating in dimethylformamide under reflux for 1 hour, afforded the corresponding 3-alkylthiopyrazolo[3,4-*d*]pyridazine derivatives **6b-d** in good yields.

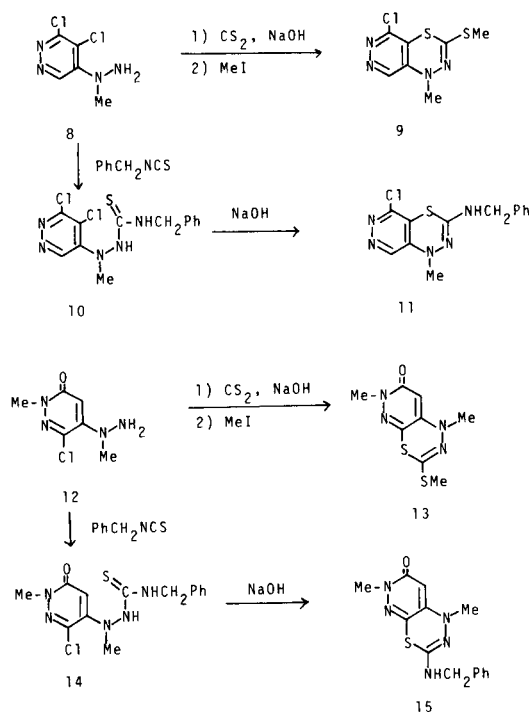
Desulfurization of 2-alkylamino or 2-anilino pyridazino[4,5-*e*][1,3,4]thiadiazine derivatives **5a-c** to the corresponding 3-aminopyrazolo[3,4-*d*]pyridazine derivatives **7a-c** was performed similarly by refluxing for 2 hours in dimethylformamide in 65-80% yields.

In contrast, any of the compounds **9**, **11**, **13** and **15** was not reacted under the similar condition (heating in di-

methylformamide) only to leave the respective starting material unchanged. The inertness for the desulfurization among these compounds, is probably due to the lack of the β -aminoenone function in the pyridazine moiety for the compound **9** and **11**, and due to the inefficiency of the function extruding sulfur from the thiadiazine moiety for the compounds **13** and **15**.

Alternatively, it might be assumed that the incorporation of β -aminoenone function into the pyridazine moiety is necessary to the desulfurization of pyridazino[4,5-*e*][1,3,4]thiadiazines, as observed from the case of the compounds **2** and **5**. Possible transient species (**2'** and **5'**) of this ring contraction are envisioned as shown in Scheme 4.

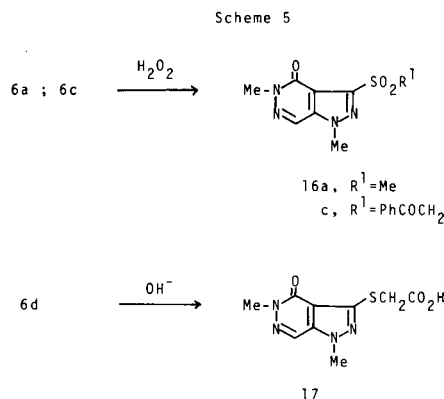
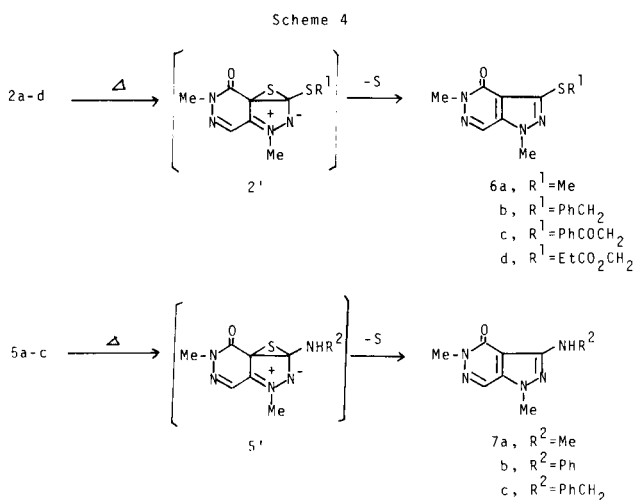
Scheme 3



Some derivatives of pyrazolo[3,4-*d*]pyridazine were prepared as follows: compound **6a** and **6c** were oxidized with 30% hydrogen peroxide in acetic acid to afford 3-methylsulfonyl and 3-phenacylsulfonyl derivatives **16a,c** in 65%

Table IV
Physical and Analytical Data for Compounds **6a-d** and **7a-c**

Compound	Appearance	Mp (°C)	Yield (%)	Molecular Formula	Analyses % Calcd./Found		
					C	H	N
6a	colorless needles	198-199	86	C ₈ H ₁₀ N ₄ OS	54.61	4.92	26.78
					54.70	4.79	26.65
6b	colorless needles	159-160	82	C ₁₄ H ₁₄ N ₄ OS	58.91	5.05	19.69
					58.72	4.93	19.57
6c	colorless needles	163-164	79	C ₁₅ H ₁₄ N ₄ O ₂ S	57.24	4.41	17.84
					57.31	4.49	17.82
6d	colorless needles	132-133	87	C ₁₁ H ₁₄ N ₄ O ₃ S	46.69	4.98	19.99
					46.80	5.00	19.84
7a	colorless needles	195-198	78	C ₈ H ₁₁ N ₅ OS	49.73	5.74	36.25
					49.82	5.80	36.12
7b	colorless needles	205-207	65	C ₁₃ H ₁₃ N ₅ O	61.17	5.13	27.43
					61.09	5.10	27.50
7c	colorless needles	168-170	80	C ₁₄ H ₁₅ N ₅ O	62.44	5.61	26.00
					62.65	5.51	26.08



and 49% yields, respectively. 3-Carboxymethylthio derivative **17** was obtained by basic hydrolysis of compound **6d** in 65% yield. The herbicidal activities of pyridazino[4,5-*e*]-[1,3,4]thiadiazine and pyrazolo[3,4-*d*]pyridazine derivatives are now under investigation and will be reported in the near future.

EXPERIMENTAL

Melting points were determined with a Yanagimoto melting point apparatus and were uncorrected. The ir spectra were recorded on a JASCO IRA-1 spectrophotometer. The ¹H-nmr spectra were taken at 60 MHz with a Hitachi R-20 spectrometer in the indicated solvents. Chemical shifts are reported in δ ppm from tetramethylsilane as an internal standard. The following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and br = broad. The mass spectra were measured with JEOL JMS-D300 mass spectrometer.

2-Alkylthio-4,7-dimethyl-4*H*-pyridazino[4,5-*e*][1,3,4]thiadiazin-8(7*H*)-ones **2a-d**. General Procedure.

To a solution of compound **1** [12] (10 mmoles) in dimethylformamide (20 ml) was added aqueous sodium hydroxide solution (1.0 g of sodium hydroxide and 3 ml of water), and the whole was stirred for 10 minutes.

Table V

Spectral Data for Compounds **6a-d** and **7a-c**

Compound	IR ν cm ⁻¹ (potassium bromide)	¹ H-NMR (deuteriochloroform): δ	
6a	1645 (CO)	2.60 (3H, s, SCH ₃), 3.76 (3H, s, NCH ₃), 3.97 (3H, s, NCH ₃), 7.93 (1H, s, H-7)	
6b	1650 (CO)	3.80 (3H, s, NCH ₃), 3.97 (3H, s, NCH ₃), 4.39 (2H, s, SCH ₂), 7.15-7.49 (5H, s, C ₆ H ₅), 7.95 (1H, s, H-7)	
6c	1640 (CO)	3.29 (3H, s, NCH ₃), 3.96 (3H, s, NCH ₃), 4.72 (2H, s, SCH ₂), 7.39-8.07 (5H, m, C ₆ H ₅), 7.97 (1H, s, H-7)	
	1660 (CO)		
6d	1655 (CO)	1.26 (3H, t, J = 7 Hz, CH ₂ CH ₃), 3.75 (3H, s, NCH ₃), 3.98 (3H, s, SCH ₂), 4.13 (2H, q, J = 7 Hz, OCH ₂ CH ₃), 7.88 (1H, s, H-7)	
	1705 (CO)		
7a	1640 (CO)	3.00 (3H, s, NCH ₃), 3.75 (3H, s, NCH ₃), 3.85 (3H, s, NCH ₃), 4.78 (1H, br, NH), 7.86 (1H, s, H-7)	
	3320 (NH)		
7b	1635 (CO)	3.78 (3H, s, NCH ₃), 3.88 (3H, s, NCH ₃), 6.95-7.71 (5H, m, C ₆ H ₅), 7.92 (1H, s, H-7)	
	3170 (NH)		
7c	1645 (CO)	3.73 (3H, s, NCH ₃), 3.80 (3H, s, NCH ₃), 4.55 (2H, d, J = 6 Hz, NCH ₂), 5.15 (1H, br, NH), 7.18-7.44 (5H, s, C ₆ H ₅), 7.82 (1H, s, H-7)	
	3360 (NH)		

Carbon disulfide (760 mg, 10 mmol) was added to the solution under stirring and the mixture was stirred for an additional 2 hours. The alkyl halide (11 mmol) was added to the reaction mixture, and the whole was stirred for 1 hour. The reaction was carried out at room temperature from beginning to end. The reaction mixture was poured into 100 ml of water and the precipitated solid was collected. Recrystallization from ethanol gave compounds **2a-d**. The results are summarized in Tables I and II.

2-Methyl-5-(1-methylhydrazino)-3(2*H*)-pyridazinone (**3**).

A solution of compound **1** (943 mg, 5 mmol) and potassium hydroxide (340 mg, 6 mmol) in methanol (50 ml) was reduced catalytically using 5% palladium on carbon (200 mg) at atmospheric pressure and room temperature. After the uptake of an equimolar amount of hydrogen, the catalyst was filtered off and the solvent was removed *in vacuo*. The product was treated with water and extracted with methylene chloride. The residue obtained upon removal of the solvent was recrystallized from ethyl acetate to give 505 mg (66% yield) of compound **3** as colorless needles, mp 185-187°; ir (potassium bromide): ν cm^{-1} 3300, 3175 (NH_2), 1615 ($\text{C}=\text{O}$); ^1H -nmr (deuteriochloroform): δ 3.10 (3H, s, NCH_3), 3.85 (3H, s, NCH_3), 4.10-4.48 (2H, br, NH_2), 5.63 (1H, d, $J = 2.9$ Hz, H-4), 8.05 (1H, d, $J = 2.9$ Hz, H-6).

Anal. Calcd. for $\text{C}_6\text{H}_{10}\text{N}_4\text{O}$: C, 46.75; H, 6.54; N, 36.34. Found: C, 46.62; H, 6.59; N, 36.21.

2-Methyl-5-(4-substituted-1-methylthiosemicarbazido)-3(2*H*)-pyridazinones **4a-c**.

A solution of compound **3** (0.77 g, 5 mmol) and methyl, phenyl or benzyl isothiocyanate (7.5 mmol) in dimethylformamide (20 ml) was heated at 80° for 3 hours. The reaction mixture was evaporated under reduced pressure and the residue was treated with ether to give crystals. Recrystallization from ethanol gave **4a**, **4b** or **4c** as described below.

Compound **4a**.

This compound was obtained in a yield of 79% (0.90 g), mp 222-223°, colorless needles; ir (potassium bromide): ν cm^{-1} 3210, 3130 (NH), 1620 ($\text{C}=\text{O}$); ^1H -nmr (dimethyl sulfoxide- d_6): δ 2.93 (3H, d, $J = 6$ Hz, NCH_3), 3.04 (3H, s, NCH_3), 3.55 (3H, s, NCH_3), 5.78 (1H, d, $J = 3$ Hz, H-4), 7.56 (1H, d, $J = 3$ Hz, H-6), 8.30 (1H, br, NH), 9.67 (1H, br, NH).

Anal. Calcd. for $\text{C}_8\text{H}_{13}\text{N}_5\text{OS}$: C, 42.28; H, 5.77; N, 30.81. Found: C, 42.27; H, 5.65; N, 31.00.

Compound **4b**.

This compound was obtained in a yield of 91% (1.32 g), mp 192-193°, colorless needles; ir (potassium bromide): ν cm^{-1} 3200, 3110 (NH), 1625 ($\text{C}=\text{O}$); ^1H -nmr (dimethyl sulfoxide- d_6): δ 3.18 (3H, s, NCH_3), 3.63 (3H, s, NCH_3), 5.89 (1H, d, $J = 3$ Hz, H-4), 7.10-7.47 (5H, m, C_6H_5), 7.61 (1H, d, $J = 3$ Hz, H-6), 8.05 (1H, br, NH), 9.93 (1H, br, NH).

Anal. Calcd. for $\text{C}_{13}\text{H}_{15}\text{N}_5\text{OS}$: C, 53.96; H, 5.23; N, 24.20. Found: C, 54.04; H, 5.24; N, 23.91.

Compound **4c**.

This compound was obtained in a yield of 77% (1.17 g), mp 219-220°, colorless needles; ir (potassium bromide): ν cm^{-1} 3220, 3120 (NH), 1625 ($\text{C}=\text{O}$); ^1H -nmr (dimethyl sulfoxide- d_6): δ 3.10 (3H, s, NCH_3), 4.79 (2H, d, $J = 6$ Hz, NCH_2), 5.85 (1H, d, $J = 3$ Hz, H-4), 7.27 (5H, s, C_6H_5), 7.61 (1H, d, $J = 3$ Hz, H-6), 8.75 (1H, br, NH), 9.73 (1H, br, NH).

Anal. Calcd. for $\text{C}_{14}\text{H}_{17}\text{N}_5\text{OS}$: C, 55.43; H, 5.65; N, 23.08. Found: C, 55.34; H, 5.38; N, 23.13.

4,7-Dimethyl-2-substituted-amino-4*H*-pyridazino[4,5-*e*][1,3,4]thiadiazine-8(7*H*)-ones **5a-c**. General Procedure.

N-Bromosuccinimide (623 mg, 3.5 mmol) was added to a suspension of **4a-c** (3 mmol) in chloroform (30 ml) by portions during 2 hours with stirring. After stirring for additional 1 hour, the solution was washed with water, then with 5% aqueous sodium hydrogen carbonate, and with water again. The residue obtained upon removal of chloroform solution was recrystallized from ethanol to give **5a-c**. The results are summarized

in Tables I and II.

5-(4-Benzyl-1-methylthiosemicarbazido)-4-chloro-2-methyl-3(2*H*)-pyridazinone (**4'c**).

A solution of compound **1** (566 mg, 3 mmol) and benzyl isothiocyanate (670 mg, 4.5 mmol) in dimethylformamide (10 ml) was heated at 80° for 3 hours. The reaction mixture was evaporated under reduced pressure and the residue was treated with ether to give crystals. Recrystallization from ethanol gave 770 mg (76%) of compound **4'c** as colorless needles, mp 208-210°; ir (potassium bromide): ν cm^{-1} 3260, 3105 (NH), 1620 ($\text{C}=\text{O}$); ^1H -nmr (dimethyl sulfoxide- d_6): δ 3.29 (3H, s, NCH_3), 3.66 (3H, s, NCH_3), 4.80 (2H, d, $J = 6$ Hz, NCH_2), 8.53 (1H, br, NH), 9.80 (1H, br, NH).

Anal. Calcd. for $\text{C}_{14}\text{H}_{15}\text{ClN}_5\text{OS}$: C, 49.77; H, 4.77; N, 20.70. Found: C, 50.01; H, 4.80; N, 20.69.

Reaction of Compound **4'c** with Sodium Hydroxide or Triethylamine.

Compound **4'c** (100 mg, 0.3 mmol) was heated at 50° for 14 hours in the presence of powdered sodium hydroxide (20 mg, 5 mmol) in dimethylformamide (5 ml). The reaction mixture was poured into ice-water (40 ml) and the solution was neutralized with dilute hydrochloric acid. The aqueous solution was extracted with chloroform. The chloroform extract was chromatographed on silica gel with chloroform as an eluent to afford 26 mg (29%) of compound **5c** and 16 mg (21%) of compound **7c** together with 41 mg (41%) of starting material **4'c**. The reaction was also carried out at 80° for 3 hours to give 47 mg (53%) of compound **5c** and 20 mg (25%) of compound **7c** together with 8 mg (8%) of starting material **4'c**. Heating of compound **4'c** (100 mg, 0.3 mmol) with sodium hydroxide (20 mg, 0.5 mmol) or triethylamine (50 mg, 0.5 mmol) in dimethylformamide (5 ml) under reflux gave 51 mg (64%) or 56 mg (70%) of compound **7c**.

3,4-Dichloro-5-(1-methylhydrazino)pyridazine (**8**).

Methylhydrazine (3.22 g, 70 mmol) was added to a solution of 3,4,5-trichloropyridazine [13] (5.6 g, 30 mmol) in methanol (35 ml) under ice-cooling. The reaction mixture was stirred at room temperature for 5 hours. The precipitated product was collected and recrystallized from ethanol to give 2.8 g (48%) of compound **8** as colorless needles, mp 132-134°; ir (potassium bromide): ν cm^{-1} 3330, 3160 (NH_2); ^1H -nmr (deuteriochloroform): δ 3.91 (2H, br, NH_2), 9.29 (1H, s, H-6).

Anal. Calcd. for $\text{C}_5\text{H}_4\text{Cl}_2\text{N}_4$: C, 31.11; H, 3.13; N, 29.02. Found: C, 30.98; H, 3.19; N, 29.11.

8-Chloro-4-methyl-2-methylthio-4*H*-pyridazino[4,5-*e*][1,3,4]thiadiazine (**9**).

Reaction of compound **8** (965 mg, 5 mmol) with carbon disulfide (380 mg, 5 mmol), methyl iodide (1.8 g, 12 mmol) and sodium hydroxide (0.5 g, 12.5 mmol) in dimethylformamide (7 ml) in a similar manner as compound **2** gave 420 mg (34%) of compound **9** as golden yellow needles, mp 190°; ir (potassium bromide): ν cm^{-1} 2980, 2920, 1525, 1335, 1150, 1095 ($\text{C}=\text{O}$); ^1H -nmr (dimethyl sulfoxide- d_6): δ 2.56 (3H, s, SCH_3), 3.46 (3H, s, NCH_3), 8.60 (1H, s, H-5).

Anal. Calcd. for $\text{C}_7\text{H}_7\text{ClN}_4\text{S}_2$: C, 34.08; H, 2.86; N, 22.71. Found: C, 34.35; H, 2.86; N, 22.96.

5-(4-Benzyl-1-methylthiosemicarbazido)-4,5-dichloropyridazine (**10**).

A solution of compound **8** (1.37 g, 7 mmol) and benzyl isothiocyanate (1.15 g, 7.7 mmol) in benzene (50 ml) was heated under reflux for 3 hours. The reaction mixture was evaporated *in vacuo* and treated with ether to give crystals. Recrystallization from ethanol afforded 1.22 g (51%) of compound **10** as orange needles, mp 174-175°; ir (potassium bromide): ν cm^{-1} 3240, 3190 (NH); ^1H -nmr (deuteriochloroform): δ 3.32 (3H, s, NCH_3), 4.48 (2H, s, NCH_2), 7.38 (5H, s, C_6H_5), 8.43 (1H, s, H-6).

Anal. Calcd. for $\text{C}_{13}\text{H}_{13}\text{Cl}_2\text{N}_5\text{S}$: C, 45.62; H, 3.83; N, 20.46. Found: C, 45.71; H, 4.00; N, 20.38.

2-Benzylamino-8-chloro-4-methyl-4*H*-pyridazino[4,5-*e*][1,3,4]thiadiazine (**11**).

A solution of compound **10** (342 mg, 1 mmol) was heated in dimethyl-

formamide (10 ml) in the presence of powdered sodium hydroxide (60 mg, 1.5 mmoles) at 100° for 3 hours. The reaction mixture was poured into ice-water and extracted with chloroform. The chloroform extract was purified by column chromatography on silica gel with chloroform as an eluent to afford 119 mg (39%) of compound **11**. Recrystallization from ethanol gave yellow needles, mp 208-209°; ir (potassium bromide): ν cm⁻¹ 3250 (NH); (C=O); ¹H-nmr (deuteriochloroform): δ 3.25 (3H, s, NCH₃), 4.30 (2H, s, NCH₂), 7.31 (5H, s, C₆H₅), 8.18 (1H, s, H-5).

Anal. Calcd. for C₁₃H₁₂ClN₂S: C, 51.06; H, 3.96; N, 22.90. Found: C, 51.21; H, 3.95; N, 22.68.

6-Chloro-2-methyl-5-(1-methylhydrazino)-3(2H)-pyridazinone (**12**).

Methylhydrazine (2.1 g, 45 mmoles) was added to a solution of 5,6-dichloro-2-methyl-3(2H)-pyridazinone [**14**] (2.6 g, 15 mmoles) in methanol (40 ml) under ice-cooling. The reaction mixture was stirred at room temperature for 5 hours. The precipitated solid was collected and recrystallized from ethanol to give 1.5 g (53%) of compound **12** as colorless needles, mp 139-140°; ir (potassium bromide): ν cm⁻¹ 3320, 3190 (NH₂), 1640 (C=O); ¹H-nmr (deuteriochloroform): δ 3.10 (3H, s, NCH₃), 3.65 (3H, s, NCH₃), 3.50-3.83 (2H, br, NH₂), 6.40 (1H, s, H-4).

Anal. Calcd. for C₆H₇ClN₄O: C, 38.21; H, 4.81; N, 29.70. Found: C, 38.20; H, 4.66; N, 29.90.

4,7-Dimethyl-2-methylthio-4H-pyridazino[4,5-e][1,3,4]thiadiazin-6(7H)-one (**13**).

Reaction of compound **12** (943 mg, 5 mmoles) with carbon disulfide (380 mg, 5 mmoles), methyl iodide (1.8 g, 12 mmoles) and sodium hydroxide (0.5 g, 12.5 mmoles) in dimethylformamide (7 ml) in a similar manner as compound **2** gave 420 mg (38%) of compound **13** as yellow needles, mp 153-150°; ir (potassium bromide): ν cm⁻¹ 1625 (C=O); ¹H-nmr (deuteriochloroform): δ 2.51 (3H, s, SCH₃), 3.29 (3H, s, NCH₃), 3.64 (3H, s, NCH₃), 5.76 (1H, s, H-5).

Anal. Calcd. for C₈H₁₀N₄OS₂: C, 39.65; H, 4.16; N, 23.12. Found: C, 39.70; H, 4.18; N, 23.23.

5-(4-Benzyl-1-methylthiosemicarbazido)-6-chloro-2-methyl-3(2H)-pyridazinone (**14**).

A solution of compound **12** (943 mg, 5 mmoles) and benzyl isothiocyanate (800 mg, 5.3 mmoles) in dimethylformamide (7 ml) was heated at 80° for 3 hours. The reaction mixture was evaporated *in vacuo* and treated with ether to give crystals. Recrystallization from ethanol afforded 1.32 g (78%) of compound **14** as colorless needles, mp 171-172°; ir (potassium bromide): ν cm⁻¹ 3210, 3110 (NH₂), 1630 (C=O); ¹H-nmr (deuteriochloroform): δ 3.04 (3H, s, NCH₃), 3.62 (3H, s, NCH₃), 4.88 (2H, d, J = 6 Hz, NCH₂), 6.66 (1H, s, H-4), 7.31 (5H, s, C₆H₅), 8.34 (1H, br, NH), 9.60 (1H, br, NH).

Anal. Calcd. for C₁₄H₁₆ClN₅OS: C, 49.77; H, 4.77; N, 20.73. Found: C, 49.69; H, 4.81; N, 20.53.

2-Benzylamino-4,7-dimethyl-4H-pyridazino[5,6-e][1,3,4]thiadiazin-6(7H)-one (**15**).

A solution of compound **14** (340 mg, 1 mmole) in dimethylformamide (5 ml) was heated in the presence of powdered sodium hydroxide (44 mg, 1.1 mmoles) at 100° for 3 hours. The reaction mixture was poured into ice-water and extracted with chloroform. The residue was obtained upon removal of chloroform was recrystallized from ethanol to give 133 mg (44%) of compound **15** as yellow needles, mp 178-180°; ir (potassium bromide): ν cm⁻¹ 3190 (NH), 1620 (C=O); ¹H-nmr (deuteriochloroform): δ 3.13 (3H, s, NCH₃), 3.60 (3H, s, NCH₃), 4.40 (2H, s, NCH₂), 5.69 (1H, s, H-5), 7.34 (5H, s, C₆H₅).

Anal. Calcd. for C₁₄H₁₅N₅OS: C, 55.80; H, 5.02; N, 23.24. Found: C, 55.58; H, 5.16; N, 23.15.

Desulfurization of Compounds **2-d** and **5a-c**. General Procedure.

A solution of compounds **2a-d** or **5a-c** (1 mmole) in dimethylformamide (10 ml) was heated under reflux for 1 hour in the case of compounds **2a-d**, or 2 hours in the case of compounds **5a-c**. The reaction mixture was evaporated under reduced pressure. The residue was recrystallized

from ethanol to give compounds **6a-d** or **7a-c**. The results are summarized in Tables IV and V.

1,5-Dimethyl-3-methylsulfonyl-1H-pyrazolo[3,4-d]pyridazin-4(5H)-one (**16a**).

A solution of compound **6a** (210 mg, 1 mmole) and 30% hydrogen peroxide (1.5 ml) in acetic acid (5 ml) was heated at 50° for 6 hours and evaporated under reduced pressure. The residue was extracted with chloroform, washed with water and dried over anhydrous magnesium sulfate. The product obtained upon removal of the solvent was recrystallized from ethanol to give 157 mg (65%) of compound **16a** as colorless prisms, mp 207-208°; ir (potassium bromide): ν cm⁻¹ 1660 (C=O), 1310, 1150 (SO₂); ¹H-nmr (dimethyl sulfoxide-d₆): δ 3.51 (3H, s, SO₂CH₃), 3.75 (3H, s, NCH₃), 4.19 (3H, s, NCH₃), 8.63 (1H, s, H-7).

Anal. Calcd. for C₈H₁₀N₄O₃S: C, 39.66; H, 4.16; N, 23.13. Found: C, 39.66; H, 4.10; N, 23.32.

1,5-Dimethyl-3-phenacysulfonyl-1H-pyrazolo[3,4-d]pyridazin-4(5H)-one (**16c**).

Reaction of compound **6c** (314 mg, 1 mmole) with 30% hydrogen peroxide (1.5 ml) in acetic acid (5 ml) was carried out similarly as compound **16a** to give 170 mg (49%) of compound **16a** as colorless prisms, mp 225-226°; ir (potassium bromide): ν cm⁻¹ 1735, 1650, (C=O), 1330 1160 (SO₂); ¹H-nmr (dimethyl sulfoxide-d₆): δ 3.77 (3H, s, NCH₃), 4.21 (3H, s, NCH₃), 5.76 (2H, s, SO₂CH₂), 7.62-8.14 (5H, m, C₆H₅), 8.79 (1H, s, H-7).

Anal. Calcd. for C₁₅H₁₄N₄O₃S: C, 52.02; H, 4.07; N, 16.18. Found: C, 52.29; H, 4.09; N, 16.36.

3-Carboxymethylthio-1,5-dimethyl-1H-pyrazolo[3,4-d]pyridazin-4(5H)-one (**17**).

A solution of compound **6d** (280 mg, 1 mmole) in methanol (5 ml) and 5% aqueous sodium hydroxide solution (2.5 ml) was heated at 100° for 3 hours. The solution was filtered to remove an insoluble solid. The filtrate was acidified by dilute hydrochloric acid. The deposited product was collected, washed with water and recrystallized from ethanol. Colorless needles (165 mg, 65%) were obtained, mp 206-208°; ir (potassium bromide): ν cm⁻¹ 3150-2600 (OH), 1720, 1625 (C=O) (C=O); ¹H-nmr (dimethyl sulfoxide-d₆): δ 3.72 (3H, s, NCH₃), 3.98 (2H, s, SCH₂), 4.04 (3H, s, NCH₃), 8.35 (1H, s, H-7), 13.24 (1H, s, OH).

Anal. Calcd. for C₈H₁₀N₄O₃S: C, 42.51; H, 3.96; N, 22.03. Found: C, 42.46; H, 4.01; N, 22.10.

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