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Synthesis of Pyridazino[4,5-*e*][1,3,4]thiadiazines and the Ring Contraction to Pyrazolo[3,4-*d*]pyridazines through Extrusion of Sulfur[1)]

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Cyclization of 2-substituted 5-[(α-bromobenzylidene)hydrazino)]-4-chloro-3(2*H*)-pyridazinones (**2**) with potassium thioacetate, followed by deacetylation, provided new ring system derivatives, 7-substituted 2-phenyl-4*H*-pyridazino[4,5-*e*][1,3,4]thiadiazin-8(7*H*)-ones (**4**). 8-Chloro and 8-amino derivatives (**10**) of the pyridazinothiadiazine ring were readily derived from 4-acetyl-2-phenyl-4*H*-pyridazino[4,5-*e*][1,3,4]thiadiazin-8(7*H*)-one (**3d**) by chlorination and subsequent amination.

Ring contraction of the 8-oxo derivatives (**4**) to 5-substituted 3-phenyl-1*H*-pyrazolo[3,4-*d*]pyridazin-4(5*H*)-ones (**6**), through extrusion of sulfur under basic or thermal conditions, was observed. A similar reaction occurred in the case of the 8-chloro and 8-amino derivatives (**10**). Probable mechanisms for these reactions and differences of reactivity between **4** and **10** are discussed.

Keywords——pyridazine; pyridazino[4,5-*e*][1,3,4]thiadiazine; pyrazolo[3,4-*d*]pyridazine; sulfur extrustion; ring contraction; potassium thioacetate

Many reports have appeared on 1,3,4-thiadiazines[2-4)] and 1,3,4-benzothiadiazines,[5-7)] but little work has been done on the synthesis of 1,3,4-thiadiazines condensed with other heterocycles.[8,9)] Previous papers from our laboratory have dealt with the conversion of 2,7-disubstituted 10*H*-dipyridazino[4,5-*b*:4′,5′-*e*][1,4]thiazine-1,6(2*H*,7*H*)-diones to 2,6-disubstituted 9*H*-dipyridazino[4,5-*b*:4′,5′-*d*]pyrrole-1,5(2*H*,6*H*)-diones by ring contraction involving base-induced extrusion of sulfur.[10)] Our observations[10)] and an interesting ring contraction in anionic 8π-ring systems[11)] have encouraged us to extend such types of reactions to the synthesis of some condensed pyridazine rings.

We wish to describe here the synthesis of 8-oxo (**4**), 8-chloro and 8-amino derivatives (**10**) of pyridazino[4,5-*e*][1,3,4]thiadiazine, a novel ring system, and their ring contraction to the corresponding pyrazolo[3,4-*d*]pyridazine derivatives (**6**, **11**) through extrusion of sulfur under basic or thermal conditions. This paper also deals with a comparison of the reactivities for desulfurization among the 8-oxo, 8-chloro and 8-amino derivatives of pyridazino[4,5-*e*]-[1,3,4]thiadiazine.

2-Substituted 5-[(α-bromobenzylidene)hydrazino]-4-chloro-3(2*H*)-pyridazinones (**2a**—**d**) were readily derived from 2-substituted 5-benzylidenehydrazino-4-chloro-3(2*H*)-pyridazinones (**1a**—**d**)[12)] by bromination using Br_2–AcOH in 40—50% yields without any other product. Reaction of **2a** with potassium thioacetate[5a)] in boiling acetonitrile for 4 h gave 4-acetyl-7-methyl-2-phenyl-4*H*-pyridazino[4,5-*e*][1,3,4]thiadiazin-8(7*H*)-one (**3a**) in 35% yield. The assigned structure for **3a** was established by the elemental analysis ($C_{14}H_{12}N_4O_2S$), mass spectrum (*m/e*: 300, M^+) and ^{1}H-NMR spectrum, in which a signal due to the acetyl group was observed at δ 2.47. Similar treatment of **2b**—**d** afforded the corresponding N^4-acetyl derivatives (**3b**—**d**) in yields of 38, 39 and 82%, respectively. A possible reaction

pathway leading to the pyridazino[4,5-*e*][1,3,4]thiadiazine derivatives (**3a—d**) is shown in Chart 1, in which a transient species (**3′**) participates, according to the proposal of Barnish and Gibson.[5a,b] Removal of the acetyl group from **3a—d** was effected by acidic treatment (HCl–EtOH) to give 7-substituted 2-phenyl-4*H*-pyridazino[4,5-*e*][1,3,4]thiadiazin-8(7*H*)-ones (**4a—d**) in good yields (Table I).

Methylation of **4a** with methyl iodide in the presence of potassium carbonate in dimethylformamide (DMF) at *ca.* 0 °C, with stirring for 24 h, gave 4,7-dimethyl-2-phenyl-4*H*-pyridazino[4,5-*e*][1,3,4]thiadiazin-8(7*H*)-one (**5a**) in good yield, though elevation of the reaction temperature reduced the yield, due to the formation of 1,5-dimethyl-3-phenyl-1*H*-pyrazolo[3,4-*d*]pyridazin-4(5*H*)-one (**7a**) as a by-product; the amount of the latter exceeded that of the former even at room temperature. This means that the ring contraction (**4a**→**6a**)

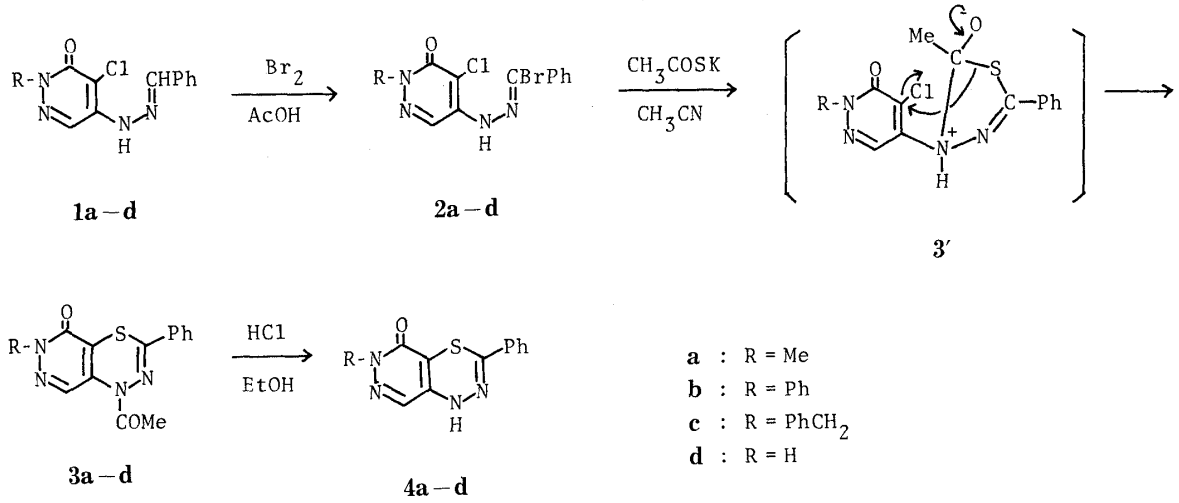

Chart 1

TABLE I. Pyridazino[4,5-*e*][1,3,4]thiadiazines (**3a—d** and **4a—d**)

Compd.	mp (°C) (Recryst. solvent)[a]	Yield (%)	Formula	Analysis (%) Calcd (Found)		
				C	H	N
3a	213—215 (CH_3CN)	35	$C_{14}H_{12}N_4O_2S$	55.99 (56.22	4.03 4.03	18.65 18.65)
3b	178—180 (AcOEt)	30	$C_{19}H_{14}N_4O_2S$	62.97 (63.16	3.89 4.00	15.46 15.22)
3c	151—152 (AcOEt)	38	$C_{20}H_{16}N_4O_2S$	63.81 (63.55	4.28 4.20	14.88 15.14)
3d	248—251 (EtOH)	82	$C_{13}H_{10}N_4O_2S$	54.54 (54.61	3.52 3.59	19.57 19.41)
4a	255—256 (EtOH)	97	$C_{12}H_{10}N_4OS$	55.80 (55.75	3.90 3.84	21.69 21.79)
4b	234—236 (EtOH)	94	$C_{17}H_{12}N_4OS$	63.73 (63.67	3.78 3.73	17.49 17.54)
4c	219—220 (EtOH)	85	$C_{18}H_{14}N_4OS$	64.65 (64.56	4.22 4.18	16.75 16.48)
4d	>300 (EtOH)	86	$C_{11}H_8N_4OS$	54.09 (54.01	3.30 3.22	22.94 23.11)

a) Compounds **3a—d** are yellow needles and **4a—d** are red needles.

TABLE II. IR, UV and ^{1}H-NMR Spectral Data for **3a—d** and **4a—d**

Compd.	IR ν_{max}^{KBr} cm^{-1}	UV λ_{max}^{EtOH} nm (log ε)	^{1}H-NMR (δ: ppm)
3a	1640 (CO)	263 (3.92)	2.47 (3H, s, $COCH_3$), 3.79 (3H, s, NCH_3), 7.33—7.95
	1690 (CO)	306 (3.80)	(5H, m, C_6H_5), 8.27 (1H, s, 5-H)[b]
3b	1645 (CO)	264 (4.15)	2.50 (3H, s, $COCH_3$), 7.25—7.85 (10H, m, $C_6H_5\times2$), 8.39
	1700 (CO)	312 (4.00)	(1H, s, 5-H)[b]
3c	1640 (CO)	263 (4.35)	2.64 (3H, s, $COCH_3$), 5.23 (2H, s, NCH_2), 7.15—7.93 (10H,
	1695 (CO)	308 (4.23)	m, $C_6H_5\times2$), 8.28 (1H, s, 5-H)[b]
3d	1650 (CO)	—[a]	2.56 (3H, s, $COCH_3$), 7.51—8.08 (5H, m, C_6H_5), 8.31 (1H,
	1690 (CO)		s, 5-H)[c]
	3160 (NH)		
4a	1620 (CO)	269 (4.11)	3.54 (3H, s, NCH_3), 7.32—7.78 (5H, m, C_6H_5), 7.36
	3300 (NH)	297 (3.98)	(1H, s, 5-H), 10.20 (1H, s, NH)[c]
4b	1605 (CO)	273 (3.99)	7.30—7.85 (11H, m, $C_6H_5\times2$ and 5-H), 10.40 (1H, s, NH)[c]
	3270 (NH)	302 (3.79)	
4c	1625 (CO)	270 (4.20)	5.14 (2H, s, NCH_2), 7.11—7.80 (10H, m, $C_6H_5\times2$), 7.47
	3260 (NH)	296 (4.06)	(1H, s, 5-H), 10.32 (1H, s, NH)[c]
4d	1610 (CO)	—[a]	7.41—7.92 (5H, m, C_6H_5), 8.12 (1H, s, 5-H), 10.18 (1H,
	3220 (NH)		s, NH)[c]

a) Insoluble in EtOH. *b*) In $CDCl_3$. *c*) In DMSO-d_6.

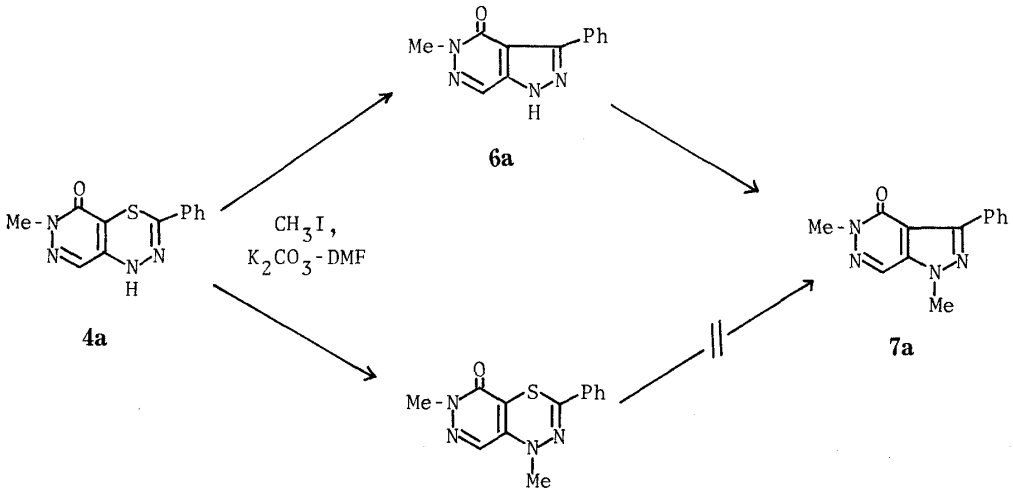

Chart 2

competes with the methylation (**4a**→**5a**) under the above reaction conditions, because the conversion (**5a**→**7a**) is virtually not observed at room temperature.

Conversion of the pyridazino[4,5-*e*][1,3,4]thiadiazine derivatives (**4a—d**) into the corresponding 5-substituted 3-phenyl-1*H*-pyrazolo[3,4-*d*]pyridazin-4(5*H*)-ones (**6a—d**) by ring contraction through extrusion of sulfur was generally performed either in basic media or thermally. The desulfurization of **4a—d** in methanolic potassium hydroxide solution proceeded rapidly, being almost complete within 1 h at room temperature or 10 min at the refluxing temperature. On acidification, high yields of the products **6a—d** were obtained (Table III). The N^4-acetyl derivatives (**3a—d**) also afforded the same products (**6a—d**) on heating under reflux for 1 h in a similar basic medium.

The ring contraction also took place thermally; *i.e.*, heating of **4a** in boiling 1,1,2,2-tetrachloroethane solution for 15 h gave the desulfurized product (**6a**) in 78% yield, while the N^4-methyl compound (**5a**) afforded the sulfur-extruded product (**7a**) in 83% yield on being refluxed in the same solvent for 4.5 h. Similar desulfurization was observed when **4a** and **5a** were heated in DMF under reflux for 4 and 2 h, respectively. Such a thermal ring contraction was also observed during melting point measurements; *e.g.*, compound **4a** melted first at 226 °C, then solidified, and melted finally at *ca.* 260 °C. These thermal desulfurizations suggest that the conversion **4a**→**6a** does not necessarily proceed with deprotonation from the substrate, although the reaction is slower than that of **5a**→**7a**.

The thermal or acid-catalyzed ring contraction of 1,3,4-thiadiazines to pyrazoles has been extensively studied.[3d,4b,5h,8] To our knowledge, however, there are only a few papers dealing with the base-induced ring contraction of 1,3,4-thiadiazines.[4f,11] A probable pathway for the ring contraction of **4a**—**d** to **6a**—**d** through base-induced extrusion of sulfur may involve the conversion of an initially generated anion (A^-), *via* a reactive intermediate containing a thiirane ring (B^-), into an anion (C^-).[10] Other analogous transient species, a

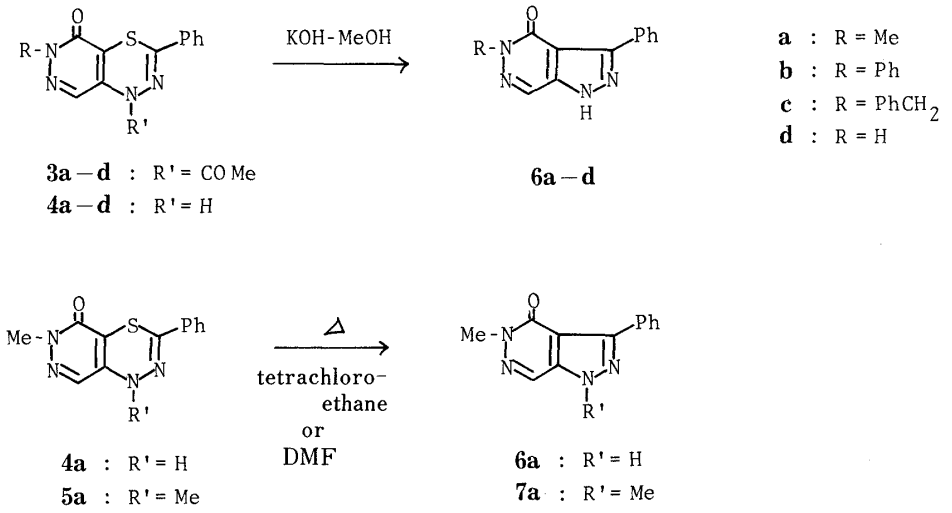

Chart 3

TABLE III. Pyrazolo[3,4-*d*]pyridazines (**6a**—**d**)

Compd.	mp (°C)[a]	Yield (%) from **3**	Yield (%) from **4**		Formula	Analysis (%) Calcd (Found) C	H	N
6a	258	65	88[b]	72[c]	$C_{12}H_{10}N_4O$	63.71 (63.64	4.46 4.50	24.76 24.96)
6b	276—278	80	83	81	$C_{17}H_{12}N_4O$	70.82 (71.03	4.20 4.21	19.43 19.53)
6c	199—200	75	83	79	$C_{18}H_{14}N_4O$	71.51 (71.65	4.67 4.57	18.53 18.49)
6d	>300	81	90	82	$C_{11}H_8N_4O$	62.26 (62.20	3.80 3.78	26.40 26.21)

a) All compounds were recrystallized from EtOH. **6a**, **c**, **d**: colorless needles. **6b**: colorless prisms.
b) Reaction for 1 h at room temperature.
c) Reaction for 10 min at refluxing temperature.

TABLE IV. IR, UV and ^{1}H-NMR Spectral Data for **6a—d**

Compd.	IR ν_{max}^{KBr} cm^{-1}	UV λ_{max}^{EtOH} nm (log ε)	^{1}H-NMR (δ: ppm)
6a	1630 (CO) 3170 (NH)	260 (4.14) 280 (4.04)	3.68 (3H, s, NCH_3), 7.30—7.50 (3H, m, *m*- and *p*-H in C_6H_5), 8.20—8.40 (2H, m, *o*-H in C_6H_5), 8.03 (1H, s, 7-H)[b]
6b	1625 (CO) 3195 (NH)	258 (4.10) 289 (4.04)	7.25—7.53 (8H, m, *m*- and *p*-H in C_6H_5, and C_6H_5), 8.10—8.30 (2H, m, *o*-H in C_6H_5), 8.48 (1H, s, 7-H)[b]
6c	1630 (CO) 3280 (NH)	261 (4.23) 281 (4.14)	5.27 (2H, s, NCH_2), 7.24 (5H, s, C_6H_5), 7.32—7.48 (3H, m, *m*- and *p*-H in C_6H_5), 8.17—8.37 (2H, m, *o*-H in C_6H_5), 8.38 (1H, s, 7-H)[b]
6d	1640 (CO) 3170 (NH)	—[a]	7.35—7.53 (3H, m, *m*- and *p*-H in C_6H_5), 8.30—8.45 (2H, m, *o*-H in C_6H_5), 8.37 (1H, s, 7-H)[c]

a) Insoluble in EtOH. *b*) In DMSO-d_6. *c*) In CF_3CO_2H.

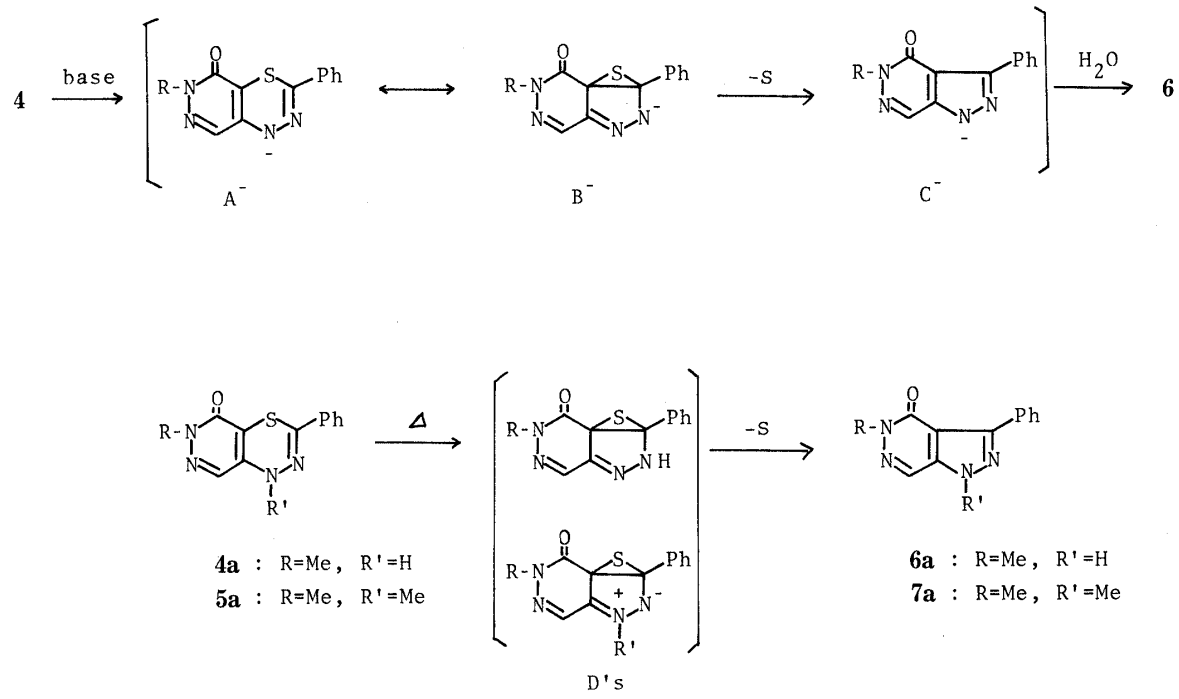

Chart 4

zwitterionic one (R′=H or Me) or its tautomer (R′=H), such as D′s, might be involved under thermal conditions.

The assigned structures for pyrazolo[3,4-*d*]pyridazines (**6a—d**) were confirmed by the elemental analyses and spectral data (IR, UV and ^{1}H-NMR) and by their methylation to **7a—c**, which were identical with samples obtained from the corresponding 2-substituted 4-chloro-5-(1-methyl-2-benzylidenehydrazino)-3(2*H*)-pyridazinones (**8a—c**) by photochemical cyclization with a 100 W high-pressure mercury lamp.[1,12] 3-Phenyl-1*H*-pyrazolo[3,4-*d*]pyridazin-4(5*H*)-one (**6d**) was readily methylated with two equivalents of methyl iodide to give 1,5-dimethyl-3-phenyl-1*H*-pyrazolo[3,4-*d*]pyridazin-4(5*H*)-one (**7a**), identical with the photocyclized product, without any contamination by its isomer.

Furthermore, the 8-chloro (**10a**) and 8-amino derivatives (**10b—d**) of pyridazino[4,5-*e*]-[1,3,4]thiadiazine similarly underwent ring contraction. Chlorination of the 4-acetyl-8-oxo

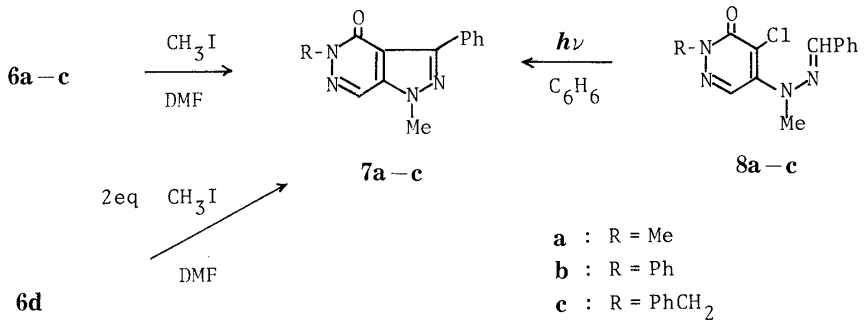

Chart 5

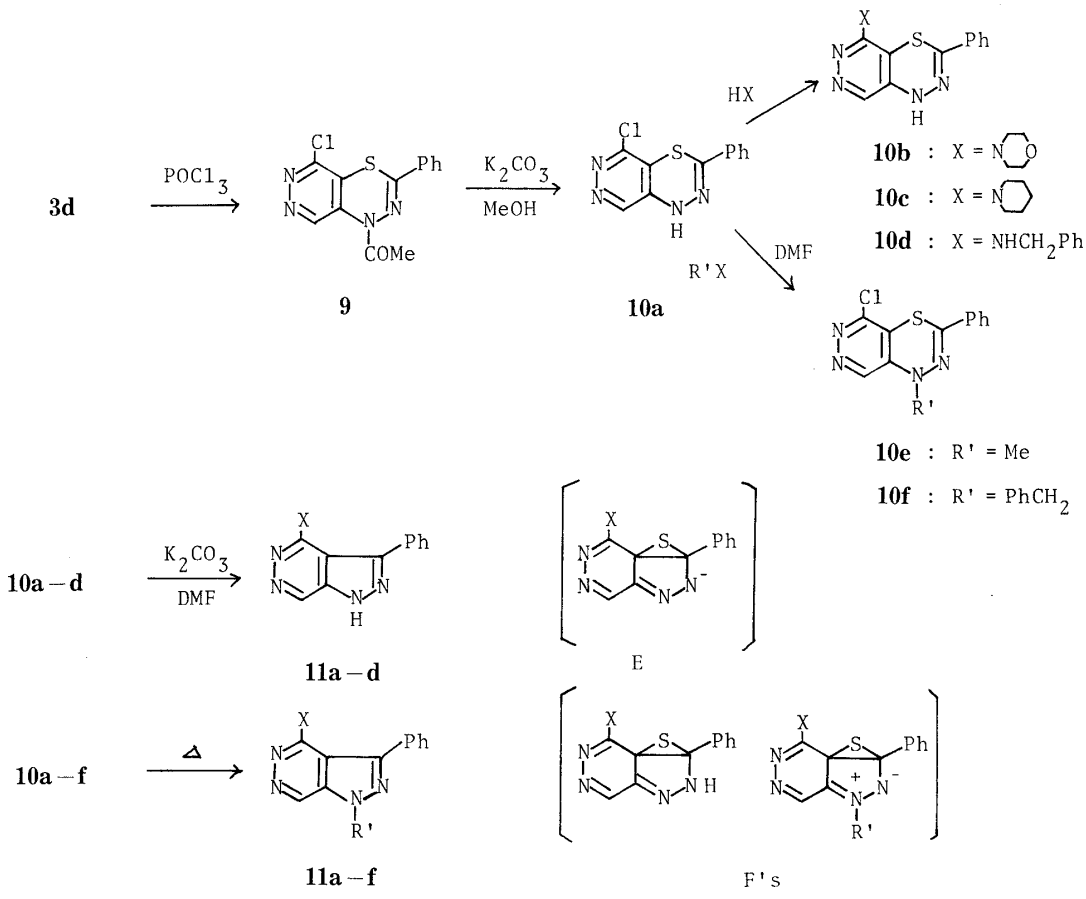

Chart 6

derivative (**3d**) with phosphorus oxychloride afforded 4-acetyl-8-chloro-2-phenyl-4*H*-pyridazino[4,5-*e*][1,3,4]thiadiazine (**9**) in 45% yield. Reaction of **9** with potassium carbonate in MeOH at room temperature gave the deacetylated product (**10a**) in 87% yield. Its N^4-methyl and N^4-benzyl derivatives (**10e**, **f**) were readily obtained by alkylation of **10a** at room temperature with methyl iodide and benzyl chloride in 68 and 40% yields, respectively. The alkylated position in **10e**, **f** was confirmed by comparison of the UV spectra with those of **10a**—**d** and by the structure of the desulfurized product **11e**, which was identical with a sample prepared by the reported procedure.[12] The 8-chloro derivative (**10a**) was heated in DMF in the presence of potassium carbonate at 100 °C for 2 h to give 4-chloro-3-phenyl-1*H*-pyrazolo[3,4-*d*]pyridazine (**11a**) in 70% yield. The need for stronger reaction conditions (100 °C, 2 h) for the desulfurization of **10a** compared to that of the 8-oxo derivatives (**4a**—**d**)

(r.t., 1 h or 100 °C, 10 min) is probably due to the lack of a β-aminoenone system in the pyridazine moiety. The 8-amino derivatives (**10b**, **c**, **d**), obtained by amination of **10a** with morpholine, piperidine and benzylamine, were also converted, through base-induced extrusion of sulfur, into the corresponding 4-amino-pyrazolo[3,4-*d*]pyridazines (**11b**, **c**, **d**) in good yields.

The desulfurization reactions of the 8-oxo-N^4-H (**4a**) and N^4-methyl (**5a**) derivatives in boiling DMF solution were almost completed in 4 h and 2 h, respectively. In contrast, neither the 8-chloro-N^4-H derivative (**10a**) nor the N^4-alkyl derivatives (**10e**, **f**) underwent desulfurization in boiling DMF solution, and the starting material was recovered. However, desulfurization proceeded on heating of **10a**—**f** without any solvent to slightly above their melting points for 10 min, to afford **11a**—**f** almost quantitatively. The resulting products were identified by thin-layer chromatographic (TLC) and ^{1}H-NMR spectral comparisons with authentic samples. Transient species possibly involved in the base-induced and thermal ring contractions are depicted as E and F's, respectively,[10] in Chart 6.

Synthesis of various other types of pyridazino[4,5-*e*][1,3,4]thiadiazine derivatives which might undergo such an extrusion of sulfur, is in progress and will be reported in the near future.

Experimental

All melting points were determined with a Yanagimoto micromelting point apparatus and are uncorrected. Infrared (IR) spectra were taken in potassium bromide disks on a JASCO IRA-I spectrophotometer. ^{1}H-Nuclear magnetic resonance (NMR) spectra were taken on a Hitachi R-20 spectrometer (60 MHz) with tetramethylsilane (TMS) as an internal standard. Ultraviolet (UV) spectra were measured in 100% EtOH with a Hitachi 323 spectrophotometer. Mass spectra (MS) were recorded on a JEOL JMS-D300 mass spectrometer.

2-Substituted 5-[(α-Bromobenzylidene)hydrazino]-4-chloro-3(2*H*)-pyridazinone (2a—d)——A solution of bromine (3.2 g, 40 mmol) in AcOH (10 ml) was added dropwise to a suspension of a 2-substituted 5-benzylidenehydrazino-4-chloro-3(2*H*)-pyridazinone (**1a**—**d**)[12] (10 mmol) in AcOH (30 ml). The reaction mixture was stirred at room temperature for 1 h, then poured into 100 ml of water. The precipitate was collected, washed with water and recrystallized from EtOH to give the corresponding product (**2a**—**d**) as described below.

2a: 1.55 g (45%), mp 198—200 °C, pale brown plates. IR ν_{max}^{KBr} cm^{-1}: 3290 (NH), 1640 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 3.78 (3H, s, NCH_3), 7.30—7.47 (3H, m, *m*- and *p*-H in C_6H_5), 7.71—7.90 (2H, m, *o*-H in C_6H_5), 8.14 (1H, s, 6-H), 8.65 (1H, br, NH). *Anal.* Calcd for $C_{12}H_{10}BrClN_4O$: C, 42.19; H, 2.95; N, 16.40. Found: C, 42.47; H, 3.01; N, 16.68.

2b: 1.70 g (42%), mp 187—189 °C, colorless needles. IR ν_{max}^{KBr} cm^{-1}: 3290 (NH), 1660 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 7.22—7.52, 7.70—7.90 (10H, m, $C_6H_5 \times 2$), 8.30 (1H, s, 6-H), 8.55 (1H, br, NH). *Anal.* Calcd for $C_{17}H_{12}BrClN_4O$: C, 50.58; H, 3.00; N, 13.88. Found: C, 50.87; H, 2.95; N, 13.97.

2c: 1.71 g (41%), mp 152—154 °C, colorless needles. IR ν_{max}^{KBr} cm^{-1}: 3270 (NH), 1635 (C=O), ^{1}H-NMR ($CDCl_3$) δ: 5.28 (2H, s, NCH_2), 7.20—7.50, 7.70—7.90 (10H, m, $C_6H_5 \times 2$), 8.19 (1H, s, 6-H), 8.74 (1H, br, NH). *Anal.* Calcd for $C_{18}H_{14}BrClN_4O$: C, 51.75; H, 3.37; N, 13.41. Found: C, 52.04; H, 3.38; N, 13.68.

2d: 1.74 g (53%), mp >300 °C, colorless needles. IR ν_{max}^{KBr} cm^{-1}: 3250 (NH), 1640 (C=O). ^{1}H-NMR (CF_3CO_2H) δ: 7.43—7.60 (3H, m, *m*- and *p*-H in C_6H_5), 7.90—8.08 (2H, m, *o*-H in C_6H_5), 8.79 (1H, s, 6-H), 9.10 (1H, br, NH). *Anal.* Calcd for $C_{11}H_8BrClN_4O$: C, 40.33; H, 2.46; N, 17.10. Found: C, 40.09; H, 2.52; N, 17.19.

General Procedure for 7-Substituted 4-Acetyl-2-phenyl-4*H*-pyridazino[4,5-*e*][1,3,4]thiadiazin-8(7*H*)-ones (3a—d)——One of the above products (**2a**—**d**) (2 mmol) was added to a boiling solution of potassium thioacetate (450 mg, 4 mmol) in acetonitrile (20 ml), and the whole was heated under reflux for 4 h. While to solution was hot, the reaction mixture was filtered to remove insoluble solids. The filtrate was concentrated to one-half of its initial volume, then cooled. The resulting precipitate was collected and recrystallized from the indicated solvent to afford the corresponding product (**3a**—**d**). The results are summarized in Tables I and II.

General Procedure for 7-Substituted 2-Phenyl-4*H*-pyridazino[4,5-*e*][1,3,4]thiadiazin-8(7*H*)-ones (4a—d)——A solution of one of **3a**—**d** (2 mmol) in conc. HCl (20 ml) and EtOH (50 ml) was refluxed for 1 h. The reaction mixture was concentrated almost to dryness *in vacuo*, and the residue was recrystallized from EtOH to give the corresponding product (**4a**—**d**). The results are summarized in Tables I and II.

4,7-Dimethyl-2-phenyl-4*H*-pyridazino[4,5-*e*][1,3,4]thiadiazin-8(7*H*)-one (5a)——Anhyd. K_2CO_3 (207 mg, 1.5 mmol) was added to a solution of methyl iodide (284 mg, 2 mmol) and **4a** (258 mg, 1 mmol) in DMF (10 ml), and the whole was stirred at 0 °C for 24 h. The reaction mixture was poured into 50 ml of water. The resulting precipitate

was collected and recrystallized from EtOH to give 210 mg (77%) of **5a** as orange needles, mp 97—99 °C. IR ν_{max}^{KBr} cm^{-1}: 1645 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 3.42 (3H, s, NCH_3), 3.75 (3H, s, NCH_3), 7.48 (1H, s, 5-H), 7.25—7.50 (3H, m, *m*- and *p*-H in C_6H_5), 7.85—7.98 (2H, m, *o*-H in C_6H_5). *Anal.* Calcd for $C_{13}H_{12}N_4OS$: C, 57.33; H, 4.44; N, 20.57. Found: C, 57.20; H, 4.63; N, 20.07.

General Procedure for Desulfurization of 3a—d and 4a—d in an Alkaline Solution. Formation of 5-Substituted 3-Phenyl-1*H*-pyrazolo[3,4-*d*]pyridazin-4(5*H*)-ones (6a—d)——a) A solution of one of **4a—d** (1 mmol) in 1% methanolic potassium hydroxide (50 ml) was heated under reflux for 10 min. The reaction mixture was evaporated under reduced pressure, and the residue was treated with 10 ml of water. The aq. solution was filtered to remove insoluble solids. The filtrate was acidified with conc. HCl. The deposited product was collected, washed with water and recrystallized from EtOH to give the corresponding product (**6a—d**). The desulfurization also proceeded at room temperature to completion within 1 h. The results are summarized in Tables III and IV.

b) A solution of one of **3a—d** (1 mmol) in 1% methanolic potassium hydroxide (50 ml) was heated under reflux for 1 h. Treatment as described above afforded the corresponding product (**6a—d**), which was identical with that obtained by procedure a).

Thermal Desulfurization of 4a——A solution of **4a** (260 mg, 1 mmol) in 1,1,2,2-tetrachloroethane (10 ml) was heated under reflux for 15 h, then evaporated *in vacuo*. The residue was recrystallized from EtOH to give 178 mg (78%) of **6a**, which was identical with the sample obtained by desulfurization of **4a** in an alkaline solution. Similarly, heating of **4a** (260 mg, 1 mmol) in DMF under reflux for 4 h afforded 192 mg (85%) of **6a**.

Thermal Desulfurization of 5a——A solution of **5a** (270 mg, 1 mmol) in 1,1,2,2-tetrachloroethane (10 ml) was heated under reflux for 4.5 h, then evaporated under reduced pressure. The resulting solid was recrystallized from EtOH to give 198 mg (83%) of **7a**. This compound was identical with the product obtained by methylation of **6a**. Heating of **5a** (270 mg, 1 mmol) in DMF under reflux for 2 h also yielded 214 mg (89%) of **7a**.

Methylation of 6a—d. Formation of 5-Substituted 1-Methyl-3-phenyl-1*H*-pyrazolo[3,4-*d*]pyridazin-4(5*H*)-ones (7a—c)——Anhyd. K_2CO_3 (207 mg, 1.5 mmol) was added to a solution of methyl iodide 213 mg, 1.5 mmol) and **6a** (226 mg, 1 mmol) in DMF (10 ml), and the whole was stirred at room temperature for 2 h. The reaction mixture was poured into 50 ml of water and extracted with benzene. The extract was washed with water and dried over anhyd. $MgSO_4$. The residue obtained by concentrating the solution was recrystallized from EtOH to give 152 mg (63%) of **7a**, mp 146 °C. **6b** (288 mg, 1 mmol) and **6c** (302 mg, 1 mmol) were methylated with methyl iodide (213 mg, 1.5 mmol) in a similar manner to give **7b** (215 mg, 71% yield, mp 198—200 °C) and **7c** (253 mg, 80% yield, mp 137—139 °C), respectively. **6d** (212 mg, 1 mmol) was methylated with methyl iodide (426 mg, 3 mmol) to give the dimethylated product **7a** (175 mg, 73% yield, mp 146 °C). These products were identical with the samples obtained by the reported procedure.[12]

4-Acetyl-8-chloro-2-phenyl-4*H*-pyridazino[4,5-*e*][1,3,4]thiadiazine (9)——A mixture of **3d** (286 mg, 1 mmol) and phosphorus oxychloride (20 ml) was warmed at 80 °C for 30 min. The residue obtained upon removal of the excess phosphorus oxychloride was poured into 20 ml of ice-water and extracted with CH_2Cl_2. The extract was washed with 5% aq. NaOH solution, then with H_2O, and dried over anhyd. $MgSO_4$. The crude product obtained by concentration of CH_2Cl_2 was recrystallized from EtOH to give 140 mg (45%) of **9** as pale yellow needles, mp 193—195 °C. IR ν_{max}^{KBr} cm^{-1}: 1690 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 2.53 (3H, s, CH_3), 7.45—8.00 (5H, m, C_6H_5), 9.55 (1H, s, 5-H). *Anal.* Calcd for $C_{13}H_{19}ClN_4OS$: C, 51.24; H, 2.98; N, 18.38. Found: C, 51.30; H, 2.91; N, 18.29.

8-Chloro-2-phenyl-4*H*-pyridazino[4,5-*e*][1,3,4]thiadiazine (10a)——Anhyd. K_2CO_3 (140 mg, 1 mmol) was added to a suspension of **9** (150 mg, 0.5 mmol) in abs. MeOH (50 ml), and the whole was stirred at room temperature for 1.5 h. After removal of excess K_2CO_3 by filtration, the reaction mixture was concentrated to dryness *in vacuo*, and 10 ml of water was added to the residue. The resulting product was collected and recrystallized from EtOH to give 114 mg (87%) of **10a** as red needles, mp 228—230 °C. IR ν_{max}^{KBr} cm^{-1}: 3120 (NH). ^{1}H-NMR (DMSO-d_6) δ: 7.28—7.52 (3H, m, *m*- and *p*-H in C_6H_5), 7.62—7.80 (2H, m, *o*-H in C_6H_5), 8.35 (1H, s, 5-H). UV λ_{max}^{EtOH} nm (log ε): 270 (3.98), 324 (3.39). *Anal.* Calcd for $C_{17}H_7ClN_4S$: C, 50.29; H, 2.68; N, 21.33. Found: C, 50.29; H, 2.75; N, 21.05.

8-Morpholino-2-phenyl-4*H*-pyridazino[4,5-*e*][1,3,4]thiadiazine (10b)——A mixture of **10a** (263 mg, 1 mmol) and morpholine (870 mg, 10 mmol) was heated at 80 °C for 12 h. The resulting product was treated with a small amount of EtOH, collected by filtration, and recrystallized from EtOH to give 253 mg (81%) of **10b** as yellow prisms, mp 235—237 °C. IR ν_{max}^{KBr} cm^{-1}: 3110 (NH). ^{1}H-NMR (DMSO-d_6) δ: 3.16—3.40 (4H, m, morpholino-H), 3.66—3.90 (4H, m, morpholino-H), 7.40—7.58 (3H, m, *m*- and *p*-H in C_6H_5), 7.73—7.91 (2H, m, *o*-H in C_6H_5), 8.11 (1H, s, 5-H). UV λ_{max}^{EtOH} nm (log ε): 266 (4.03), 320 (3.44). *Anal.* Calcd for $C_{15}H_{15}N_5OS$: C, 57.49; H, 4.82; N, 22.35. Found: C, 57.43; H, 4.89; N, 22.34.

2-Phenyl-8-piperidino-4*H*-pyridazino[4,5-*e*][1,3,4]thiadiazine (10c)——A mixture of **10a** (263 mg, 1 mmol) and piperidine (860 mg, 10 mmol) was heated at 70 °C for 9 h. The resulting product was treated with a small amount of EtOH and collected by filtration. Recrystallization from EtOH gave 186 mg (60%) of **10c** as yellow prisms, mp 226—228 °C. IR ν_{max}^{KBr} cm^{-1}: 3100 (NH). ^{1}H-NMR (DMSO-d_6) δ: 1.63—1.87 (6H, m, piperidino-H), 3.19—3.45 (4H, m, piperidino-H), 7.40—7.51 (3H, m, *m*- and *p*-H in C_6H_5), 7.78—7.85 (2H, m, *o*-H in C_6H_5), 8.29 (1H, s, 5-H). UV λ_{max}^{EtOH} nm (log ε): 267 (4.11), 321 (3.39). *Anal.* Calcd for $C_{16}H_{17}N_5S$: C, 61.71; H, 5.50; N, 22.49. Found: C, 61.43; H, 5.46; N, 22.51.

8-Benzylamino-2-phenyl-4*H*-pyridazino[4,5-*e*][1,3,4]thiadiazine (10d)——A mixture of **10a** (263 mg, 1 mmol) and benzylamine (1.1 g, 10 mmol) was heated at 90 °C for 24 h, then 50 ml of chloroform was added. The chloroform solution was washed with water and dried over anhyd. $MgSO_4$. The residue obtained upon removal of the chloroform was recrystallized from EtOH to give 202 mg (61%) of **10d** as yellow needles, mp 185—187 °C. IR ν_{max}^{KBr} cm^{-1}: 3110 (NH). ^{1}H-NMR (DMSO-d_6) δ: 4.75 (2H, d, J=6 Hz, -NHC$\underline{H}_2$-), 7.24—8.00 (10H, m, $C_6H_5 \times 2$), 8.15 (1H, s, 5-H). UV λ_{max}^{EtOH} nm (log ε): 265 (4.06), 325 (3.32). *Anal.* Calcd for $C_{18}H_{15}N_5S$: C, 64.84; H, 4.53; N, 21.00. Found: C, 64.86; H, 4.60; N, 20.78.

8-Chloro-4-methyl-2-phenyl-4*H*-pyridazino[4,5-*e*][1,3,4]thiadiazine (10e)——Anhyd. K_2CO_3 (280 mg, 2 mmol) was added to a solution of methyl iodide (462 mg, 3 mmol) and **10a** (263 mg, 1 mmol) in 10 ml of DMF, and the whole was stirred at room temperature for 5 h. The reaction mixture was poured into 100 ml of water. The separated solid was collected and recrystallized from EtOH to give 185 mg (68%) of **10e** as reddish-brown needles, mp 225—226 °C. ^{1}H-NMR (DMSO-d_6) δ: 3.52 (3H, s, NCH_3), 7.49—7.66 (3H, m, *m*- and *p*-H in C_6H_5), 8.21 (1H, s, 5-H). UV λ_{max}^{EtOH} nm (log ε): 269 (4.14) 323 (3.29). *Anal.* Calcd for $C_{12}H_9ClN_4S$: C, 52.08; H, 3.28; N, 20.24. Found: C, 52.06; H, 3.22; N, 20.23.

4-Benzyl-8-chloro-2-phenyl-4*H*-pyridazino[4,5-*e*][1,3,4]thiadiazine (10f)——Compound **10a** (263 mg, 1 mmol) was reacted with benzyl chloride (139 mg, 1.1 mmol) and anhyd. K_2CO_3 (280 mg, 2 mmol) in DMF (10 ml) in the same manner described for compound **10e** to give 144 mg (40%) of **10f** as dark red needles (from EtOH), mp 191—192 °C. ^{1}H-NMR ($CDCl_3$) δ: 4.96 (2H, s, NCH_2), 7.27—7.90 (10H, m, $C_6H_5 \times 2$), 8.29 (1H, s, 5-H). UV λ_{max}^{EtOH} nm (log ε): 271 (4.04), 319 (3.29). *Anal.* Calcd for $C_{18}H_{13}ClN_4S$: C, 61.27; H, 3.71; N, 15.88. Found: C, 61.09; H, 3.72; N, 15.84.

General Procedure for Desulfurization of 10a—d with Potassium Carbonate. Formation of 4-Substituted 3-Phenyl-1*H*-pyrazolo[3,4-*d*]pyridazines (11a—d)——A mixture of **10a**, **10b**, **10c** or **10d** (1 mmol) and anhyd. K_2CO_3 (210 mg, 1.5 mmol) in DMF (10 ml) was heated at 100 °C for 2 h. After removal of excess K_2CO_3 by filtration, the reaction mixture was concentrated *in vacuo*. The residue was dissolved in 5% aq. NaOH solution (30 ml) to remove insoluble solids. The filtrate was acidified with conc. HCl. The deposited product was collected, washed with H_2O and recrystallized from EtOH to give **11a**, **11b**, **11c** or **11d** as described below.

11a: 161 mg (70%), mp >300 °C, colorless plates. IR ν_{max}^{KBr} cm^{-1}: 3140 (NH). ^{1}H-NMR (DMSO-d_6) δ: 7.32—7.51 (3H, m, *m*- and *p*-H in C_6H_5), 8.24—8.42 (2H, m, *o*-H in C_6H_5), 8.26 (1H, s, 7-H). *Anal.* Calcd for $C_{11}H_7ClN_4$: C, 57.28; H, 3.06; N, 24.29. Found: C, 57.36; H, 3.07; N, 24.15.

11b: 240 mg (85%), mp >300 °C, colorless plates. IR ν_{max}^{KBr} cm^{-1}: 3110 (NH). ^{1}H-NMR (CF_3CO_2H) δ: 3.55—3.91 (8H, m, morpholino-H), 7.52—7.78 (5H, m, C_6H_5), 9.20 (1H, s, 7-H). *Anal.* Calcd for $C_{15}H_{15}N_5O$: C, 64.04; H, 5.37; N, 24.89. Found: C, 64.13; H, 5.44; N, 24.94.

11c: 194 mg (70%), mp >300 °C, colorless plates. IR ν_{max}^{KBr} cm^{-1}: 3090 (NH). ^{1}H-NMR (CF_3CO_2H) δ: 1.63—1.71 (6H, m, piperidino-H), 3.44—3.67 (4H, m, piperidino-H), 7.49—7.75 (5H, m, C_6H_5), 9.00 (1H, s, 7-H). *Anal.* Calcd for $C_{16}H_{17}H_5$: C, 68.80; H, 6.13; N, 25.07. Found: C, 68.87; H, 6.09; N, 24.92.

11d: 255 mg (85%), mp 266—268 °C, colorless needles. IR ν_{max}^{KBr} cm^{-1}: 3120 (NH). ^{1}H-NMR (DMSO-d_6) δ: 4.72 (2H, s, NCH_2), 7.10—7.78 (10H, m, $C_6H_5 \times 2$), 8.85 (1H, s, 7-H). *Anal.* Calcd for $C_{18}H_{15}N_5$: C, 71.74; H, 5.02; N, 23.24. Found: C, 71.69; H, 4.98; N, 23.29.

Thermal Desulfurization of 10a—f. Formation of 4-Substituted 3-Phenyl-1*H*-pyrazolo[3,4-*d*]pyridazines (11a—f)——a) Compounds **10a—d** (30 mg) were each heated at a temperature slightly above the melting point for 10 min in an NMR sampling tube, then cooled. DMSO-d_6 (0.3 ml) was added to the sampling tube. The chemical shifts in the ^{1}H-NMR spectrum and the *Rf* values on silica gel thin-layer chromatography (TLC) were identical with those of the corresponding sample obtained from **10a—d** by desulfurization with K_2CO_3.

b) Heating of **10e** (30 mg) in a sampling tube in the same manner described for **10a—d** afforded **11e**. This compound was identical with a sample prepared by the reported procedure.[12]

c) Compound **10f** (176 mg, 0.5 mmol) was heated at 200 °C (nearly 10 °C higher than its melting point) without any solvent. The red crystals became colorless and sulfur sublimed. The residue was recrystallized from EtOH to give 133 mg (83%) of **11f** as colorless needles, mp 150—151 °C. ^{1}H-NMR ($CDCl_3$) δ: 5.32 (2H, s, NCH_2), 7.07—7.43, 8.20—8.36 (10H, m, $C_6H_5 \times 2$), 9.38 (1H, s, 7-H). *Anal.* Calcd for $C_{18}H_{13}ClN_4$: C, 67.40; H, 4.08; N, 17.47. Found: C, 67.49; H, 4.16; N, 17.38.

References and Notes

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