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Conversion of Dipyridazino[4,5-*b*:4',5'-*e*][1,4]thiazines into Dipyridazino[4,5-*b*:4',5'-*d*]pyrroles through a Base-Induced Extrusion of Sulfur

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A novel ring contraction for 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 (**4'a**—**c**) into the corresponding 2,6-disubstituted 9*H*-dipyridazino[4,5-*b*:4',5'-*d*]pyrrole-1,5(2*H*,6*H*)-diones (**7'a**—**c**), through a base-induced extrusion of sulfur, is described. Heating of **4'a**—**c** in dimethylformamide in the presence of potassium carbonate smoothly afforded **7'a**—**c**, respectively, in good yields, although neither 2,8-dimethyl-10*H*-dipyridazino[4,5-*b*:4',5'-*e*][1,4]thiazine-1,9(2*H*,8*H*)-dione (**5'a**), nor 3,7-dimethyl-10*H*-dipyridazino[4,5-*b*:4',5'-*e*][1,4]thiazine-4,6(3*H*,7*H*)-dione (**6'a**) was susceptible to similar reaction conditions.

The mechanism of the ring contraction, which may involve an intermediate (anion, C[−]) containing a thiirane ring, is also discussed.

Keywords—pyridazine; dipyridazino[1,4]thiazine; dipyridazino[4,5-*b*:4',5'-*d*]pyrrole; sulfur extrusion; ring contraction; Smiles rearrangement; photochemical cyclization

In 1974 Castle¹⁾ reported the first synthesis of several dipyridazino[1,4]thiazines, in which both benzenoid rings of the parent phenothiazine were replaced by pyridazines. During the course of our studies on the synthesis of 3(2*H*)-pyridazinone derivatives,²⁾ we have observed the concurrent formation of two isomeric dipyridazino[4,5-*b*:4',5'-*e*][1,4]thiazine derivatives (**4a** + **5a**, **4a** + **6a**) accompanied with a unique dipyridazino[4,5-*b*:4',5'-*d*]pyrrole derivative (**7a**).³⁾ In the previous paper³⁾ we described the unusual formation of 9-benzyl-2,6-dimethyl-9*H*-dipyridazino[4,5-*b*:4',5'-*d*]pyrrole-1,5(2*H*,6*H*)-dione (**7a**) in the condensation between 4-amino-5-mercapto-2-methyl-3(2*H*)-pyridazinone (**1a**) and 4,5-dichloro-2-methyl-3(2*H*)-pyridazinone (**3a**) by heating in dimethylformamide (DMF) in the presence of potassium carbonate with subsequent benzylation, together with the formation of 10-benzyl-2,7-dimethyl-10*H*-dipyridazino[4,5-*b*:4',5'-*e*][1,4]thiazine-1,6(2*H*,7*H*)-dione (**4a**) and 10-benzyl-2,8-dimethyl-10*H*-dipyridazino[4,5-*b*:4',5'-*e*][1,4]thiazine-1,9(2*H*,8*H*)-dione (**5a**). Similar formation of **7a**, **4a**, and 10-benzyl-3,7-dimethyl-10*H*-dipyridazino[4,5-*b*:4',5'-*e*][1,4]thiazine-4,6(3*H*,7*H*)-dione (**6a**) in the condensation of **3a** with 5-amino-4-mercapto-2-methyl-3(2*H*)-pyridazinone (**2a**) under similar reaction conditions, and an independent synthesis of **7a** by photochemical cyclization, were also reported. A possible mechanism for the unusual formation of **7a** was proposed, but without much experimental evidence.

In the present work, we have further investigated the mechanism of the unusual formation of 2,6-disubstituted 9-benzyl-9*H*-dipyridazino[4,5-*b*:4',5'-*d*]pyrrole-1,5(2*H*,6*H*)-diones (**7a**—**c**) during the condensation reactions, and we propose a pathway involving the conversion of **4'a**—**c** into **7'a**—**c** through a base-induced extrusion of sulfur, with subsequent benzylation of **7'a**—**c** into **7a**—**c**. There have been several reports concerned with desulfurization of 1,4-thiazine and phenothiazine derivatives to pyrrole and the carbazole derivatives respectively, by pyrolysis in the presence of copper⁴⁾ or by treatment with lithium in tetrahydrofuran at moderate temperatures.⁵⁾ However, to the best of our knowledge, base-

Chart 1

induced extrusion of sulfur in the phenothiazine ring has not been described previously, although similar ring contractions of 1,3,4-thiadiazine to pyrazole,⁶⁾ and 1,3-thiazine anion to pyrrole anion,⁷⁾ have been reported.

To prove the proposed pathway, **4'a** $\rightarrow$ **7'a** $\rightarrow$ **7a**, for the unusual formation of **7a** in the condensation between **1a** and **3a** or **2a** and **3a**, with subsequent benzylation,³⁾ all of the following criteria should be met. (i') The process **4a** $\rightarrow$ **7a** does not occur on heating for 3 h at 150 °C in DMF in the presence of potassium carbonate. (ii') The process **4'a** $\rightarrow$ **7'a** does not occur on heating (150 °C) in DMF in the absence of potassium carbonate. (iii') The process **4'a** $\rightarrow$ **7'a** occurs only under the reaction conditions defined in (i'). (iv') **4'a** is readily formed and is stable enough for conversion into **7'a** to occur during the condensation.

Experimental tests of these criteria were carried out to prove the proposed pathway, with the following results. (i) Compound **4a** was almost completely recovered without any formation of **7a**. (ii) Compound **4'a** was almost quantitatively recovered and was converted satisfactorily into **4a** by benzylation. (iii) Compound **4'a** was smoothly converted into **7'a**, which was led satisfactorily to **7a** by benzylation. (iv) Based on smooth cyclization *via* Smiles rearrangement of 5-(4-benzylamino-2,3-dihydro-2-methyl-3-oxo-pyridazinyl) 5'-(4'-chloro-2',3'-dihydro-2'-methyl-3'-oxo-pyridazinyl) sulfide (**10a**) to **4a** as described below, formation of **4'a** as the precursor of **7'a** during the condensation can be reasonably assumed.

The crucial step in the condensation, conversion of the dipyridazino[4,5-*b*:4',5'-*e*]-[1,4]thiazines (**4'a**—**c**) into the dipyridazino[4,5-*b*:4',5'-*d*]pyrroles (**7'a**—**c**) through a base-induced extrusion of sulfur, was supported by the following results. (a) Formation of 5-(2-substituted 4-benzylamino-2,3-dihydro-3-oxo-pyridazinyl) 5'-(2'-substituted 4'-chloro-2',3'-dihydro-3'-oxo-pyridazinyl) sulfides (**10a**—**c**). (b) Cyclization of the sulfides (**10a**—**c**) to the corresponding **4a**—**c** *via* Smiles rearrangement, followed by debenylation to 2,7-disubstituted 10*H*-dipyridazino[4,5-*b*:4',5'-*e*][1,4]thiazine-1,6(2*H*,7*H*)-diones (**4'a**—**c**). (c) Conversion of **4'a**—**c** into **7'a**—**c** through a base-induced extrusion of sulfur.

Chart 2

Chart 3

The sulfide (10a), instead of 10'a, was chosen as a starting material in this design, because of easier handling and facile removal of the benzyl group from the product. 4-Benzylamino-5-mercapto-2-methyl-3(2H)-pyridazinone (9a) reacted with 3a in an alkaline solution (stirring for 1 h at room temperature) to afford the sulfide (10a) in 52% yield. Similarly, 2,2'-diphenyl sulfide (10b: 52% yield) and 2,2'-dibenzyl sulfide (10c: 54% yield) were derived from the

corresponding 2-substituted 4-benzylamino-5-mercapto-3(2*H*)-pyridazinones, **9b** and **9c**, respectively. The structure of the sulfide (**10a**) deduced from the spectral data was confirmed by the fact that the benzylamino sulfide (**11**), derived from **10a** by benzylamination, yielded 4-benzylamino-2-methyl-3(2*H*)-pyridazinone (**12**), without any contamination by the corresponding 5-benzylamino derivative (**13**), upon desulfurization with Raney nickel. 2-Substituted 4,5-dichloro-3(2*H*)-pyridazinones (**3a—c**) are readily convertible to 2-substituted 4-benzylamino-5-chloro-3(2*H*)-pyridazinones (**8a—c**) by benzylamination in boiling toluene, with little formation of the corresponding 5-benzylamino-4-chloro isomers (**8'a—c**),⁸⁾ and heating of **8a—c** with sodium hydrosulfide in DMF afforded 2-substituted 4-benzylamino-5-mercapto-3(2*H*)-pyridazinones (**9a—c**) satisfactorily.

Chart 4

The sulfide (**10a**) was heated for 2 h with stirring in 10% sodium hydroxide solution to afford a single product, 10-benzyl-2,7-dimethyl-10*H*-dipyridazino[4,5-*b*:4',5'-*e*][1,4]-thiazine-1,6(2*H*,7*H*)-dione (**4a**), in 79% yield. On similar treatment of the sulfide **10b** and **10c**, the cyclization proceeded smoothly to afford the 10-benzyl-2,7-diphenyl derivative (**4b**) and the 2,7,10-tribenzyl derivative (**4c**) in 63% and 81% yields, respectively. Debenzylation of these dipyridazino[1,4]thiazines (**4a—c**) was carried out without difficulty, by the use of a Lewis acid (AlCl_3 in warm toluene)²⁾ or by heating in hydrochloric acid, to yield the 2,7-disubstituted 10*H*-dipyridazino[4,5-*b*:4',5'-*e*][1,4]thiazine-1,6(2*H*,7*H*)-diones, **4'a** (60% yield), **4'b** (87% yield), and **4'c** (92% yield). These dipyridazino[1,4]thiazines (**4'a—c**), upon benzylation, reverted to the original dipyridazino[1,4]thiazine derivatives (**4a—c**) without any other alkylated product. Conversion of **4'a—c** into **7'a—c** was successfully achieved through a base-induced extrusion of sulfur, as follows: **4'a** was heated at 150 °C with potassium carbonate in DMF with constant stirring while the color of the reaction mixture changed from red to green, and heating was continued for 3 h to complete the reaction. Appropriate work-up of the resulting mixture afforded 2,6-dimethyl-9*H*-dipyridazino[4,5-*b*:4',5'-*d*]pyrrole-1,5(2*H*,6*H*)-dione (**7'a**) in 71% yield. Similar treatment of **4'b** and **4'c** smoothly gave the corresponding dipyridazino[4,5-*b*:4',5'-*d*]pyrroles, **7'b** (74% yield) and **7'c** (91% yield). The assigned structures for **7'a—c** were established by the spectral and elemental analysis data, and were supported by the empirical fact that the *N*⁹-benzyl derivatives (**7a—c**) were formed by an independent synthesis based on photochemical cyclization of *N*-benzyl-*N,N'*-(2,2'-disubstituted 3,3'-dioxo-2,3,2',3'-tetrahydro-4,5')di-

TABLE I. Dipyridazino[4,5-*b*:4',5'-*d*]pyrroles (7' and 7)

Compd. ^{a)}	R ¹	R ²	Yield (%)	mp (°C)	Formula	Analysis (%)		
						Calcd (Found)		
						C	H	N
7'a	CH ₃	H	71	> 300	C ₁₀ H ₉ N ₅ O ₂	51.94 (51.96)	3.92 (3.91)	30.29 (30.11)
7'b	C ₆ H ₅	H	74	> 300	C ₂₀ H ₁₃ N ₅ O ₂	67.60 (67.57)	3.69 (3.56)	19.71 (19.68)
7'c	PhCH ₂	H	81	> 300	C ₂₂ H ₁₇ N ₅ O ₂	68.92 (68.62)	4.47 (4.48)	18.27 (18.17)
7a	CH ₃	PhCH ₂	69	215—216	C ₁₇ H ₁₅ N ₅ O ₂	63.54 (63.42)	4.70 (4.69)	21.79 (21.56)
7b	C ₆ H ₅	PhCH ₂	73	213—214	C ₂₇ H ₁₉ N ₅ O ₂	72.80 (72.81)	4.30 (4.24)	15.72 (15.59)
7c	PhCH ₂	PhCH ₂	68	195—196	C ₂₉ H ₂₃ N ₅ O ₂	73.56 (73.43)	4.90 (4.93)	14.79 (14.92)

a) All compounds were recrystallized from EtOH to give colorless needles except 7a (colorless plates).

TABLE II. IR, UV and ¹H-NMR Spectra Data for 7'a—c and 7a—c

Compd.	IR ν _{max} ^{KBr} cm ⁻¹		UV λ _{max} ^{EtOH} nm (log ε)	¹ H-NMR (δ: ppm) ^{a)}
	NH	CO		
7'a	3180	1635 1650	—	3.70 (6H, s, NCH ₃), 8.43 (1H, s, C ⁸ -H), 8.75 (1H, s, C ⁴ -H)
7'b	3160	1640 1670	—	7.64 (10H, s, C ₆ H ₅ × 2), 8.65 (1H, s, C ⁸ -H), 9.02 (1H, s, C ⁴ -H)
7'c	3210	1640 1660	—	5.73 (4H, s, NCH ₂ × 2), 7.39 (10H, s, C ₆ H ₅ × 2), 8.94 (1H, s, C ⁸ -H), 9.27 (1H, s, C ⁴ -H)
7a	—	1650 1670	252 (4.25) 261 (4.24) 281 (4.19) 312 (4.09)	3.89 (3H, s, NCH ₃), 3.94 (3H, s, NCH ₃), 6.09 (2H, s, NCH ₂), 7.31 (5H, s, C ₆ H ₅), 8.15 (1H, s, C ⁸ -H), 8.79 (1H, s, C ⁴ -H)
7b	—	1655 1665	250 (4.32) 259 (4.26) 275 (4.37) 310 (4.02)	6.17 (2H, s, NCH ₂), 7.39—7.80 (15H, m, C ₆ H ₅ × 3), 8.39 (1H, s, C ⁸ -H), 8.98 (1H, s, C ⁴ -H)
7c	—	1650 1660	249 (4.30) 256 (4.22) 282 (4.05) 316 (3.92)	5.43, 5.49, 6.01 (each 2H, each s, each NCH ₂), 7.28—7.39 (15H, m, C ₆ H ₅ × 3), 8.18 (1H, s, C ⁸ -H), 8.86 (1H, s, C ⁴ -H)

a) Solvents: 7'a, 7'b and 7'c in CF₃CO₂H; 7a, 7b and 7c in CDCl₃.

pyridazinylamines (15a—c) in acetone with a 100 W high-pressure mercury lamp, each in fairly good yield (7a, 67%; 7b, 82%; 7c, 73%). Each amine (15a—c) was derived from any of 4a—c by desulfurization with Raney nickel, and also by condensation between 5-chloro-2-methyl-3(2*H*)-pyridazinone (14) and 4-benzylamino-2-methyl-3(2*H*)-pyridazinone (12). This proves the assigned structures (4a—c) for the dipyridazino[1,4]thiazines obtained by cyclization through Smiles rearrangement of the sulfide (10a—c) and consequently confirms the structures of the related compounds (7a—c).

a : $R^1 = CH_3$, b : $R^1 = C_6H_5$, c : $R^1 = PhCH_2$; $R^2 = PhCH_2$

Chart 5

Chart 6

Chart 7

One of the most likely pathways for the ring contraction of the dipyridazino[1,4]thiazines (**4'a**—**c**) to the dipyridazino-pyrroles (**7'a**—**c**), through a base-induced extrusion of sulfur, may be depicted as a process in which an initially generated anion (A^-) is converted, *via* a transition state (B^-), into an intermediate (C^-), which in turn leads to a final anion (D^-).

Although the rate-determining step of the reaction remains to be identified, it might be reasonable to presume that the ease with which the set of anions, A^- — D^- , is generated during the process could control the overall rate of this conversion. The two carbon atoms, designated as C^α and C^β , both linked the sulfur atom in **4'a**—**c** might change their electron density dynamically, or the electron density on the former atom might be increased (more nucleophilic) while that on the latter might be decreased (more electrophilic), depending on the state of the surrounding basic medium. Interestingly, molecules lacking such a pair of carbon atoms (C^α and C^β), *e.g.*, **5'a** and **6'a**, as well as **16**, **17** and **18**,⁹⁾ were indeed not susceptible to the reaction.

Synthesis of alternative types of dipyridazino[1,4]thiazines, **5'a**—**c** and **6'a**—**c**, and additional types of polyazaphenothiazine derivatives which might undergo such a base-induced extrusion of sulfur, are 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 spectrometer. ¹H-Nuclear magnetic resonance (NMR) spectra were taken on a Hitachi R-20 spectrophotometer (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.

10-Benzyl-2,7-dimethyl-10H-dipyridazino[4,5-*b*:4',5'-*e*][1,4]thiazine-1,6(2*H*,7*H*)-dione (4a)—A suspension of **10a** (1.0 g, 2.6 mmol) in 10% aq. NaOH (20 ml) was heated at 120 °C for 2 h, then cooled. The resulting precipitate was collected by filtration, washed with H₂O and recrystallized from EtOH to give 0.7 g (79%) of **4a** as red needles, mp 185–186 °C. IR $\nu_{\max}^{\text{KBr}}$ cm⁻¹: 1630, 1640 (CO). UV $\lambda_{\max}^{\text{EtOH}}$ nm (log ϵ): 236 (4.03), 271 (4.15), 315 (4.10). ¹H-NMR (CDCl₃) δ : 3.67 (3H, s, NCH₃), 3.70 (3H, s, NCH₃), 5.27 (2H, s, NCH₂), 7.30 (1H, s, C⁹-H), 7.41 (1H, s, C⁴-H), 7.30–7.60 (5H, m, C₆H₅). MS *m/e*: 353 (M⁺). Anal. Calcd for C₁₇H₁₅N₅O₂S: C, 57.77; H, 4.27; N, 19.81. Found: C, 57.67; H, 4.43; N, 19.52.

10-Benzyl-2,7-diphenyl-10H-dipyridazino[4,5-*b*:4',5'-*e*][1,4]thiazine-1,6(2*H*,7*H*)-dione (4b)—**10b** (1.0 g, 1.9 mmol) was heated in 10% aq. NaOH (20 ml) as described above to give 0.54 g (63%) of **4b** as reddish-purple needles, mp 170 °C. IR $\nu_{\max}^{\text{KBr}}$ cm⁻¹: 1640, 1660 (CO). UV $\lambda_{\max}^{\text{EtOH}}$ nm (log ϵ): 232 (4.33), 269 (4.39), 337 (4.36). ¹H-NMR (CDCl₃) δ : 5.28 (2H, s, NCH₂), 7.47 (15H, s, C₆H₅ × 3), 7.59 (1H, s, C⁹-H), 7.61 (1H, s, C⁴-H). MS *m/e*: 477 (M⁺). Anal. Calcd for C₂₇H₁₉N₅O₂S: C, 67.91; H, 4.01; N, 14.66. Found: C, 67.71; H, 3.95; N, 14.54.

2,7,10-Tribenzyl-10H-dipyridazino[4,5-*b*:4',5'-*e*][1,4]thiazine-1,6(2*H*,7*H*)-dione (4c)—**10c** (1.1 g, 2 mmol) was heated in DMF (30 ml) in the presence of anhyd. K₂CO₃ at 120 °C for 2 h. The reaction mixture was poured into H₂O. The precipitated solid was extracted with CH₂Cl₂ and dried over anhyd. MgSO₄. The residue obtained upon removal of the solvent was recrystallized from EtOH to give 0.82 g (81%) of **4c** as orange prisms, mp 156 °C. IR $\nu_{\max}^{\text{KBr}}$ cm⁻¹: 1640, 1650 (CO). UV $\lambda_{\max}^{\text{EtOH}}$ nm (log ϵ): 255 (4.33), 270 (4.24), 321 (4.20). ¹H-NMR (CDCl₃) δ : 5.17 (6H, s, NCH₂ × 3), 7.27 (15H, s, C₆H₅ × 3), 7.31 (2H, s, C⁴-H and C⁹-H). MS *m/e*: 505 (M⁺). Anal. Calcd for C₂₉H₂₃N₅O₂S: C, 68.89; H, 4.58; N, 13.85. Found: C, 68.79; H, 4.56; N, 13.88.

2,7-Dimethyl-10H-dipyridazino[4,5-*b*:4',5'-*e*][1,4]thiazine-1,6(2*H*,7*H*)-dione (4'a)—**4a** (3.5 g, 10 mmol) was added to a solution of anhyd. AlCl₃ (6.0 g, 50 mmol) in dry toluene (200 ml) with stirring, and the whole was warmed at 60 °C for 5 h, then cooled. Water was added, and the precipitated solid was collected, washed with H₂O and recrystallized from AcOH to give 1.5 g (60%) of **4'a** as reddish-purple crystals, mp > 300 °C. IR $\nu_{\max}^{\text{KBr}}$ cm⁻¹: 3270, 3360 (NH), 1620, 1635 (CO). ¹H-NMR (CF₃CO₂H) δ : 3.78 (6H, s, NCH₃ × 2), 7.35 (1H, s, C⁹-H), 7.55 (1H, s, C⁴-H). MS *m/e*: 263 (M⁺). Anal. Calcd for C₁₀H₉N₅O₂S: C, 45.62; H, 3.45; N, 26.60. Found: C, 46.03; H, 3.50; N, 26.58.

2,7-Diphenyl-10H-dipyridazino[4,5-*b*:4',5'-*e*][1,4]thiazine-1,6(2*H*,7*H*)-dione (4'b)—**4b** (1.43 g, 3 mmol) in dry toluene (150 ml) was reacted with anhyd. AlCl₃ (0.6 g, 5 mmol) as described above to give 1.0 g (87%) of **4'b** as reddish-purple crystals, mp > 300 °C. IR $\nu_{\max}^{\text{KBr}}$ cm⁻¹: 3310, 3230 (NH), 1610, 1625 (CO). ¹H-NMR (CF₃CO₂H) δ : 7.02 (10H, s, C₆H₅ × 2), 7.05 (1H, s, C⁹-H), 7.31 (1H, s, C⁴-H). MS *m/e*: 387 (M⁺). Anal. Calcd for C₂₀H₁₃N₅O₂S: C, 62.00; H, 3.38; N, 18.08. Found: C, 61.79; H, 3.33; N, 17.81.

2,7-Dibenzyl-10H-dipyridazino[4,5-*b*:4',5'-*e*][1,4]thiazine-1,6(2*H*,7*H*)-dione (4'c)—A solution of **4c** (1.5 g, 3 mmol) in conc. HCl (20 ml) and AcOH (40 ml) was refluxed for 3 h, then cooled. The resulting precipitate was

collected and washed with H₂O to give 1.1 g (92%) of **4'**c as reddish-purple crystals, mp > 300 °C. IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 3260, 3320 (NH), 1620, 1630 (CO). ¹H-NMR (CF₃CO₂H) δ : 5.38 (4H, s, NCH₂ × 2), 7.39 (10H, s, C₆H₅ × 2), 7.45 (1H, s, C⁹-H), 7.77 (1H, s, C⁴-H). MS *m/e*: 415 (M⁺). Anal. Calcd for C₂₂H₁₇N₅O₂S: C, 63.60; H, 4.12; N, 16.86. Found: C, 63.65; H, 4.00; N, 16.94.

Benzylation of 4'a—c—Anhyd. K₂CO₃ (345 mg, 2.5 mmol) was added to a solution of benzyl chloride (80 mg, 0.65 mmol) and **4'a**, **4'b** or **4'c** (0.5 mmol) in DMF (10 ml), and the whole was heated at 50 °C for 2 h. The reaction mixture was poured into H₂O (100 ml) and extracted with CH₂Cl₂. The extract was washed with H₂O and dried over MgSO₄. The residue obtained by concentrating the solution was recrystallized from EtOH to give **4a** (125 mg, 71% yield, mp 185–186 °C, red needles), **4b** (150 mg, 63% yield, mp 170 °C, reddish-purple needles), or **4c** (172 mg, 68% yield, mp 156 °C, orange prisms). These products were identical (mp, thin-layer chromatography (TLC), IR and ¹H-NMR) with the samples obtained from **10a—c** via Smiles rearrangement.

2,6-Disubstituted 9H-Dipyridazino[4,5-b:4',5'-d]pyrrole-1,5(2H,6H)-diones (7'a—c)—**4'a**, **4'b** or **4'c** (1 mmol) was heated in DMF (20 ml) in the presence of anhyd. K₂CO₃ (690 mg, 5 mmol) at 150 °C for 3 h. After removal of excess K₂CO₃ by filtration, the reaction mixture was concentrated to dryness *in vacuo*, and the residue was treated with H₂O (10 ml). The aq. solution was acidified with conc. HCl to precipitate a white solid, which was collected, washed with H₂O, and dissolved in 5% aq. NaOH (10 ml). The solution was filtered to remove an insoluble solid. The alkaline solution was acidified with conc. HCl. The deposited product was collected, washed with H₂O, and recrystallized from EtOH to give **7'a**, **7'b** or **7'c**. The results are summarized in Tables I and II.

2,6-Disubstituted 9-Benzyl-9H-dipyridazino[4,5-b:4',5'-d]pyrrole-1,5(2H,6H)-diones (7a—c)—Anhyd. K₂CO₃ (690 mg, 5 mmol) was added to a solution of benzyl chloride (160 mg, 1.3 mmol) and **7'a**, **7'b** or **7'c** (1 mmol) in DMF (20 ml), and the whole was heated at 80 °C for 5 h. The reaction mixture was poured into H₂O (100 ml) and extracted with CH₂Cl₂. The extract was washed with H₂O and dried over MgSO₄. The residue obtained by concentrating the solution was recrystallized from EtOH to afford **7a**, **7b** or **7c**. The results are summarized in Tables I and II.

5-(2-Substituted 4-Benzylamino-2,3-dihydro-3-oxo-pyridazinyl) 5'-(2'-Substituted 4'-Chloro-2',3'-dihydro-3'-oxo-pyridazinyl) Sulfide (10a—c)—**10a**: A solution of **3a** (1.79 g, 10 mmol) in DMF (25 ml) was added dropwise to a solution of **9a** (2.44 g, 10 mmol) and KOH (0.62 g, 11 mmol) in MeOH (20 ml). The reaction mixture was stirred for 1 h at room temperature. The precipitated solid was collected, washed with H₂O and recrystallized from EtOH to give 1.10 g (52%) of **10a** as yellow needles, mp 185–186 °C. IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 3320 (NH), 1620, 1660 (CO). ¹H-NMR (CDCl₃) δ : 3.72 (3H, s, NCH₃), 3.82 (3H, s, NCH₃), 4.95 (2H, s, NCH₂), 6.99 (1H, s, C⁶-H), 7.31 (5H, s, C₆H₅), 7.49 (1H, s, C^{6'}-H). Anal. Calcd for C₁₇H₁₆ClN₅O₂S: C, 52.37; H, 4.14; N, 17.96. Found: C, 52.26; H, 4.13; N, 17.97. **10b**: Reaction of **3b** (1.21 g, 5 mmol) with **9b** (1.55 g, 5 mmol) and KOH (0.31 g, 5.5 mmol) was carried out as in the case of **10a** to afford **10b** (1.34 g, 52%) as yellow needles, p 190 °C. IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 3270 (NH), 1620, 1640 (CO). ¹H-NMR (DMSO-*d*₆) δ : 5.07 (2H, s, NCH₂), 7.23–7.55 (15H, m, C₆H₅ × 3), 7.39 (1H, s, C⁶-H), 7.78 (1H, s, C^{6'}-H). Anal. Calcd for C₂₇H₂₀ClN₅O₂S: C, 63.09; H, 3.92; N, 13.62. Found: C, 63.28; H, 4.01; N, 13.72. **10c**: Reaction of **3c** (1.28 g, 5 mmol) with **9c** (1.62 g, 5 mmol) and KOH (0.31 g, 5.5 mmol) was carried out as described above to yield **10c** (1.46 g, 54%) as yellow needles, mp 175–177 °C. IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 3240 (NH), 1615, 1630 (CO). ¹H-NMR (DMSO-*d*₆) δ : 4.90, 5.10, 5.28 (each 2H, each s, each NCH₂), 7.01–7.38 (15H, m, C₆H₅ × 3), 7.39 (1H, s, C⁶-H), 7.54 (1H, s, C^{6'}-H). Anal. Calcd for C₂₉H₂₄ClN₅O₂S: C, 64.26; H, 4.46; N, 12.92. Found: C, 64.00; H, 4.58; N, 12.87.

Reaction of 3a—c with Benzylamine—A solution of **3a**, **3b** or **3c** (10 mmol) and benzylamine (30 mmol) in toluene (50 ml) was refluxed for 3 h. The precipitated benzylamine hydrochloride was filtered off and the filtrate was concentrated *in vacuo*. The residue was chromatographed on silica gel with C₆H₆ as an eluent to afford first **8a—c** and then **8'a—c** as described below.

i) **4-Benzylamino-5-chloro-2-methyl-3(2H)-pyridazinone (8a)**: 1.50 g (60%), colorless plates (EtOH), mp 98 °C. IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 3310 (NH). Anal. Calcd for C₁₂H₁₂ClN₃O: C, 57.72; H, 4.48; N, 16.83. Found: C, 57.79; H, 4.85; N, 16.91. **5-Benzylamino-4-chloro-2-methyl-3(2H)-pyridazinone (8'a)**: 0.18 g (7%), colorless needles (EtOH), mp 183–185 °C. IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 3320 (NH). Anal. Calcd for C₁₂H₁₂ClN₃O: C, 57.72; H, 4.84; N, 16.83. Found: C, 57.81; H, 5.01; N, 16.72.

ii) **4-Benzylamino-5-chloro-2-phenyl-3(2H)-pyridazinone (8b)**: 1.20 g (38%), colorless plates (EtOH), mp 109–110 °C. IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 3290 (NH). Anal. Calcd for C₁₇H₁₄ClN₃O: C, 65.49; H, 4.53; N, 13.48. Found: C, 65.52; H, 4.34; N, 13.63. **5-Benzylamino-4-chloro-2-phenyl-3(2H)-pyridazinone (8'b)**: 0.89 g (28%), colorless needles (EtOH), mp 213–215 °C. IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 3320 (NH). Anal. Calcd for C₁₇H₁₄ClN₃O: C, 65.49; H, 4.53; N, 13.48. Found: C, 65.39; H, 4.62; N, 13.37.

iii) **2-Benzyl-4-benzylamino-5-chloro-3(2H)-pyridazinone (8c)**: 2.35 g (67%), colorless plates (EtOH), mp 124–126 °C. IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 3280 (NH). Anal. Calcd for C₁₈H₁₆ClN₃O: C, 66.36; H, 4.95; N, 12.90. Found: C, 66.12; H, 4.98; N, 13.10. **2-Benzyl-5-benzylamino-4-chloro-3(2H)-pyridazinone (8'c)**: 0.47 g (14%), colorless needles (EtOH), mp 130–131 °C. IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 3310 (NH). Anal. Calcd for C₁₈H₁₆ClN₃O: C, 66.36; H, 4.95; N, 12.90. Found: C, 66.46; H, 5.18; N, 12.98.

2-Substituted 4-Benzylamino-5-mercapto-3(2H)-pyridazinones (9a—c)—**9a**: **8a** (5.0 g, 20 mmol) was added to a solution of sodium hydrosulfide (70% purity, 4.8 g, 60 mmol) in DMF (50 ml), and the whole was heated at 90 °C for

10 h. The reaction mixture was concentrated *in vacuo*. Water (100 ml) was added to the residue and the aq. solution was acidified with conc. HCl to precipitate a yellow solid, which was collected, washed with H₂O and dissolved in dil. NaOH solution. The solution was filtered to remove an insoluble solid. The alkaline solution was acidified with conc. HCl, and the deposited solid was collected, washed with H₂O and recrystallized from EtOH to give 3.6 g (71%) of **9a** as yellow needles, mp 157–158 °C. IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 3290 (NH), 2530 (SH). *Anal.* Calcd for C₁₂H₁₃N₃OS: C, 58.28; H, 5.29; N, 16.99. Found: C, 58.49; H, 5.18; N, 17.12.

9b:8b (3.1 g, 10 mmol) was reacted with 70% sodium hydrosulfide (2.4 g, 30 mmol) in DMF (40 ml) as described above to give 1.1 g (32%) of **9b** as yellow needles, mp 176–177 °C. IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 3295 (NH), 2500 (SH). *Anal.* Calcd for C₁₇H₁₅N₃OS: C, 66.00; H, 4.89; N, 13.58. Found: C, 66.08; H, 4.56; N, 13.70.

9c:8c (3.3 g, 10 mmol) reacted with 70% sodium hydrosulfide (2.4 g, 30 mmol) in DMF (30 ml) as described above to afford **9c** (1.6 g, 49%) as yellow needles, mp 150–151 °C. IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 3295 (NH), 2520 (SH). *Anal.* Calcd for C₁₈H₁₇N₃OS: C, 66.85; H, 5.30; N, 12.99. Found: C, 66.59; H, 5.00; N, 12.80.

Bis(4-benzylamino-2,3-dihydro-2-methyl-3-oxo-5-pyridazinyl) Sulfide (11)—**10a** (1.17 g, 3 mmol) was heated under reflux with benzylamine (1.1 g, 10 mmol) in toluene (50 ml) for 6 h, then cooled. The resulting precipitate was collected and recrystallized from EtOH to give 0.52 g (38%) of **11** as colorless needles, mp 200–202 °C. IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 3205 (NH), 1610 (CO). ¹H-NMR (CDCl₃) δ : 3.63 (6H, s, NCH₃ $\times$ 2), 4.88 (4H, s, NCH₂ $\times$ 2), 6.60 (2H, br, NH $\times$ 2, D-exchangeable), 7.23 (10H, s, C₆H₅ $\times$ 2), 7.77 (2H, s, C⁶-H and C^{6'}-H). *Anal.* Calcd for C₂₄H₂₄N₆O₂S: C, 62.59; H, 5.25; N, 18.25. Found: C, 62.45; H, 5.10; N, 18.27.

Desulfurization of 11 with Raney Ni—A suspension of **11** (276 mg, 0.6 mmol) in DMF (10 ml) with 0.5 g of Raney Ni (W-2) was heated at 150 °C for 10 h and the reaction mixture was filtered while hot. The Raney Ni residue was washed with hot DMF. The combined DMF solution was evaporated to dryness *in vacuo* and the residue was recrystallized from cyclohexane to give 210 mg (83%) of 4-benzylamino-2-methyl-3(2H)-pyridazinone (**12**) as colorless needles, mp 86–87 °C. IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 3270 (NH), 1635 (CO). ¹H-NMR (CDCl₃) δ : 3.80 (3H, s, NCH₃), 4.96 (2H, s, NCH₂), 5.95 (1H, d, *J* = 6 Hz, C⁵-H), 6.38 (1H, br, NH, D-exchangeable), 7.39 (5H, s, C₆H₅), 7.57 (1H, d, *J* = 6 Hz, C⁶-H). *Anal.* Calcd for C₁₂H₁₃N₃O: C, 66.95; H, 6.09; N, 19.52. Found: C, 67.08; H, 6.21; N, 19.41.

Desulfurization of 4a–c with Raney Ni—A suspension of **4a**, **4b** or **4c** (0.5 mmol) with Raney Ni (W-2, 1 g) in DMF (50 ml) was refluxed with stirring for 5 h. The reaction mixture was filtered and the filtrate was evaporated to dryness *in vacuo*. The residue was recrystallized from EtOH to give **15a**, **15b** or **15c** as described below.

15a (120 mg, 74%): mp 204–206 °C, colorless needles. ¹H-NMR (CDCl₃) δ : 3.70 (3H, s, NCH₃), 3.87 (3H, s, NCH₃), 5.00 (2H, s, NCH₂), 6.19 (1H, d, *J* = 4 Hz, C⁴-H), 7.08 (1H, d, *J* = 6 Hz, C⁵-H), 7.34 (5H, s, C₆H₅), 7.43 (1H, d, *J* = 4 Hz, C⁶-H), 7.78 (1H, d, *J* = 6 Hz, C^{6'}-H). *Anal.* Calcd for C₁₇H₁₇N₅O₂: C, 63.15; H, 5.30; N, 21.66. Found: C, 63.25; H, 5.16; N, 21.90.

15b (106 mg, 50%): mp 206–207 °C, colorless needles. ¹H-NMR (CDCl₃) δ : 4.98 (2H, s, NCH₂), 6.05 (1H, d, *J* = 4 Hz, C⁴-H), 7.02 (1H, d, *J* = 6 Hz, C⁵-H), 7.11–7.39 (15H, m, C₆H₅ $\times$ 3), 7.47 (1H, d, *J* = 4 Hz, C⁶-H), 7.61 (1H, d, *J* = 6 Hz, C^{6'}-H). *Anal.* Calcd for C₂₇H₂₁N₅O₂: C, 72.47; H, 4.73; N, 15.65. Found: C, 72.36; H, 4.31; N, 15.56.

15c (135 mg, 57%): mp 201–202 °C, colorless needles. ¹H-NMR (CDCl₃) δ : 4.91, 5.02, 5.19 (each 2H, each s, each NCH₂), 6.10 (1H, d, *J* = 4 Hz, C⁴-H), 6.98 (1H, d, *J* = 6 Hz, C⁵-H), 7.09–7.38 (15H, m, C₆H₅ $\times$ 3), 7.49 (1H, d, *J* = 4 Hz, C⁶-H), 7.58 (1H, d, *J* = 6 Hz, C^{6'}-H). *Anal.* Calcd for C₂₉H₂₅N₅O₂: C, 73.25; H, 5.30; N, 14.73. Found: C, 73.44; H, 5.21; N, 14.89.

An Unequivocal Synthesis of 15a—A mixture of 4-benzylamino-2-methyl-3(2H)-pyridazinone (**12**) (215 mg, 1 mmol) and 5-chloro-2-methyl-3(2H)-pyridazinone (**14**) (154 mg, 1 mmol) was heated at 150 °C in DMF (30 ml) in the presence of anhyd. K₂CO₃ (414 mg, 3 mmol) for 5 h. The reaction mixture was poured into H₂O and extracted with CHCl₃. The residual solid obtained by concentration of the CHCl₃ solution was recrystallized from EtOH to give **15a** (139 mg, 43%). This compound was identical (mp, TLC, IR and ¹H-NMR) with the sample obtained from **4a** by desulfurization with Raney Ni.

Photochemical Cyclization of 15a–c to 7a–c—A solution of **15a** (100 mg) in acetone (150 ml) was irradiated with a 100 W high-pressure mercury lamp surrounded by a water-cooled Pyrex filter at room temperature for 1 h. Upon removal of the solvent, the residue was recrystallized from EtOH to give 67 mg (67%) of **7a** as colorless plates, mp 215–216 °C. **15b** (50 mg) and **15c** (120 mg) were irradiated in a similar manner to give **7b** (36 mg, 72% yield, mp 213–214 °C, colorless needles) and **7c** (88 mg, 73% yield, mp 195–196 °C, colorless needles), respectively. These products were identical (mp, TLC, IR and ¹H-NMR) with the samples obtained from **4'a–c** by desulfurization followed by benzylation.

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