[Chem. Pharm. Bull. 18(1) 147—156 (1970)]

UDC 547.852.7.07

Synthesis of Pyridazine Derivatives with Sulfur-Containing Substituent. II.[1] A Novel Cyclization Furnishing the Concurrent Formation of 2,7-Dibenzyldipyridazo-[4,5-*b*:4′,5′-*e*]-1,4-dithiin-1,6(2*H*,7*H*)-dione and 2,8-Dibenzyldipyridazo[4,5-*b*:4′,5′-*e*]-1,4-dithiin-1,9(2*H*,8*H*)-dione. (1)[2]

KENJI KAJI, MASAYUKI KUZUYA[3]
and RAYMOND N. CASTLE[3a)]

Gifu College of Pharmacy[3]

(Received July 14, 1969)

2-Benzyl-4-chloro-5-mercapto-3(2*H*)-pyridazinone (**1**) was heated in ethanol under reflux for 10 hours to form concurrently 2,7-dibenzyldipyridazo[4,5-*b*:4′,5′-*e*]-1,4-dithiin-1,6(2*H*,7*H*)-dione (Ia) (57% in yield) and 2,8-dibenzyldipyridazo[4,5-*b*:4′,5′-*e*]-1,4-dithiin-1,9(2*H*,8*H*)-dione (IIa) (14% in yield). Assignment of the two products to the corresponding structures is established by their physico-chemical constants and chemical behaviors. The concurrent formation of the dipyridazo[4,5-*b*:4′,5′-*e*]-1,4-dithiin-1,6(2*H*,7*H*)-dione and the -1,9(2*H*,8*H*)-dione were observed in, not only heating 4-chloro-5-mercapto-3(2*H*)-pyridazinones (**1**—**3**) in polar solvent, but warming 4-mercapto-5-chloro-3(2*H*)-pyridazinones (**4**—**6**) in the presence of potassium carbonate in DMF. For the interpretation of the reaction, keto-thioketo carbenes as active intermediate species and a reversible interconversion among them are suggested on the basis of the fact that there was non-existence of an equilibrium between the two compounds, such as Ia and IIa, under the reaction condition and a trapping keto-thioketo carbene species as 2-phenylimino-5-benzylpyridazo[4,5-*d*]-1,3-dithiol-4(5*H*)-one (IVa) (14% in yield) along with the major products, (Ia) and (IIa), was furnished by warming **1** with phenylisothiocyanate in the presence of triethylamine in dry benzene. On the contrary, participation of a reversible interconversion between Ia and IIa, to a considerable extent, with the concurrent formation of them in the case of benzylation of either Ib or IIb, by warming with benzylchloride in the presence of potassium carbonate in DMF at 80°, might not be neglected, because an attempted approach to an equilibrium between Ia and IIa in a similar reaction condition except the use of benzylchloride realized, whereas non-existence of an equilibrium between Ib and IIb in the similar reaction condition was observed.

During the course of the investigation of the synthesis of the pyridazine derivatives,[1,4,5] an interest in the formation and the chemical and physiological properties of the dipyridazo-[4,5-*b*:4′5′-*e*]-1,4-dithiin-1,6(2*H*,7*H*)-dione derivatives[6] led us to a further search of the ring system.

In an earlier paper[7] dealing with the formation and cleavage of the compounds, it was shown 4,5-dichloro- and 2-phenyl-4,5-dichloro-3(2*H*)-pyridazinone were heated with sodium hydrosulfide in ethanol under reflux to afford dipyridazo[4,5-*b*:4′,5′-*e*]-and 2,7-diphenyldipyri-

---

[1] Part I: K. Kaji, H. Mori, I. Yoshida, T. Ichii, H. Nagashima and R.N. Castle, *Gifu Yakkadaigaku Kiyo*, **17**, 66 (1967).

[2] Presented in part at the 88th Annual Meeting of Pharmaceutical Society of Japan, Tokyo University, April 1968.

[3] Location: *492–36, Mitahora, Gifu*; *a*) Present address: *Department of Chemistry, University of New Mexico, Albuquerque, New Mexico, U.S.A.*

[4] R.N. Castle and K. Kaji, *J. Heterocyclic Chem.*, 2, 463 (1965).

[5] R.N. Castle and K. Kaji, *Tetrahedron Letters*, **1963**, 393.

[6] R.N. Castle and K. Kaji, *Naturwissenschaften*, **51**, 38 (1964).

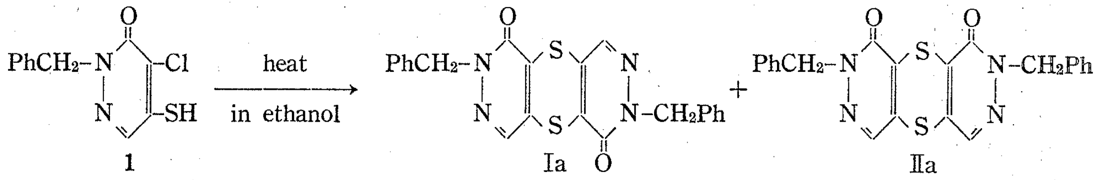
[7] R.N. Castle, K. Kaji and D. Wise, *J. Heterocyclic Chem.*, 3, 541 (1966).

dazo[4,5-*b*:4′,5′-*e*]-1,4-dithiin-1,6(2*H*,7*H*)-dione respectively, in fairly good yields. K. Dury has also reported the synthesis of N,N-disubstituted dipyridazo[4,5-*b*:4′,5′-*e*]-1,4-dithiin-1,6-(2*H*,7*H*)-diones without experimental details.[8]

A novel cyclization furnishing the concurrent formation of 2,7-dibenzyldipyridazo[4,5-*b*:4′,5′-*e*]-1,4-dithiin-1,6(2*H*,7*H*)-dione and 2,8-dibenzyldipyridazo[4,5-*b*:4′,5′-*e*]-1,4-dithiin-1,9-(2*H*,8*H*)-dione resulted by heating 2-benzyl-4-chloro-5-mercapto-3(2*H*)-pyridazinone in ethanol and the analogous reaction with a proposal of the reactive intermediates for these reactions are described in this paper.

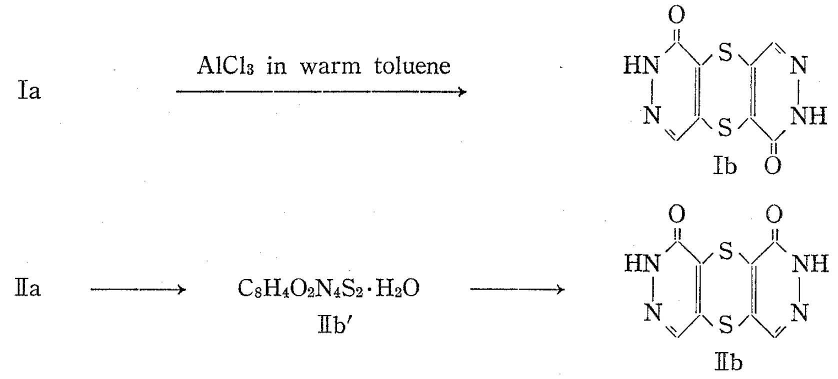
2-Benzyl-4-chloro-5-mercapto-3(2*H*)-pyridazinone (**1**) was heated under reflux in abs. ethanol for 10 hours and the products were chromatographed over silica gel to give the two compounds with same elemental analysis value for $C_{22}H_{16}O_2N_4S_2$, *i.e.*, yellowish orange needles (A), mp 265° and 57% in yield, and reddish purple needles (B), mp 263° and 14% in yield.

The structures of the isomeric compounds, (A) and (B), were confirmed to be assignable to 2,7-dibenzyldipyridazo[4,5-*b*:4′,5′-*e*]-1,4-dithiin-1,6(2*H*,7*H*)-dione (Ia) and 2,8-dibenzyldipyridazo[4,5-*b*:4′,5′-*e*]-1,4-dithiin-1,9(2*H*,8*H*)-dione (IIa) respectively on the basis of the following physico-chemical constants and chemical experimental facts.



These two compounds showed similar characteristic figures in IR, UV, NMR and Mass Spectrum, (A): IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1608 (CON<), UV $\lambda_{\max}^{\text{EtOH}}$ mμ (log ε): 319 (4.04), 338 (3.99), NMR (in $CDCl_3$)τ: 4.58 (4H, singlet, N–CH_2–) and 2.23 (2H, singlet, ring-H) and Mass Spectrum *m/e*: 432 (M^+). (B): IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1618 (CON<), UV $\lambda_{\max}^{\text{EtOH}}$ mμ (log ε): 318 (4.12), NMR (in $CDCl_3$)τ: 4.56 (4H, singlet, N–CH_2–) and 2.21 (2H, singlet, ring-H) and Mass Spectrum *m/e*: 432 (M^+), however, remarkable different values in dipole moment, (A): 0.3D and (B): 10.2D.

Each of these compounds, (A) and (B), was easily debenzylated by using anhydrous aluminum chloride in warm toluene solution to form dipyridazo[4,5-*b*:4′,5′-*e*]-1,4-dithiin-1,6-(2*H*,7*H*)-dione (Ib) and dipyridazo[4,5-*b*:4′,5′-*e*]-1,4-dithiin-1,9(2H,8*H*)-dione (IIb) *via* its monohydrate (IIb′) respectively in fairly good yield.

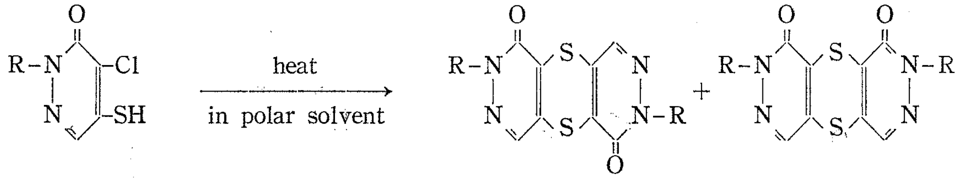


Although an exclusive reversion of each compound, (Ib) or (IIb) by benzylation to the original compound, (Ia) or (IIa), respectively was difficulty effected by use of benzylchloride in the presence of potassium carbonate in dimethylformamide (DMF), which the formation of a mixture of the compounds, (Ia) and (IIa), always occurred as it will be mentioned in detail below.

---

[8] K. Dury, *Angew. Chem.*, 77, 282 (1964).

Concurrent formation of dipyridazo[4,5-*b*:4′,5′-*e*]-1,4-dithiin-1,6(2*H*,7*H*)-dione (Ib) and 1,9(2*H*,8*H*)-dione (IIb), as well as 2,7-dimethyldipyridazo[4,5-*b*:4′,5′-*e*]-1,4-dithiin-1,6(2*H*,7*H*)-dione (Ic) and 2,8-dimethyldipyridazo[4,5-*b*:4′,5′-*e*]-1,4-dithiin-1,9(2*H*,8*H*)-dione (IIc), was also observed with the product proportion in yield, Ib: 58% and IIb: 20%, as well as Ic: 40% and IIc: 24%, when 4-chloro-5-mercapto-3(2*H*)-pyridazinone (**2**) or 2-methyl-4-chloro-5-mercapto-3(2*H*)-pyridazinone (**3**) was heated in a polar solvent, ethanol, ethylene glycol or DMF.



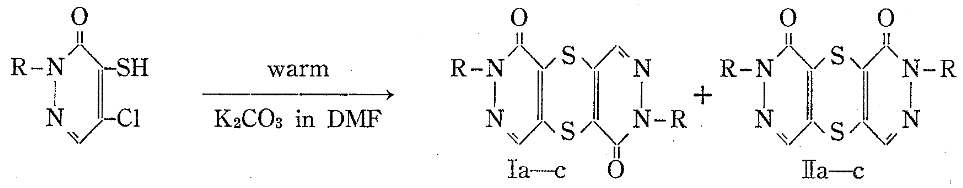
2 : R=H
3 : R=Me

Ib : R=H
Ic : R=Me

IIb : R=H
IIc : R=Me

Structural assignment of the product (Ic), to the 1,6(2*H*,7*H*)-dione system and (IIc) to the 1,9(2*H*,8*H*)-dione system, were carried by comparison of C=O absorption in IR and UV patterns with those of the compounds, Ia and IIa. Ic: IR ν_{max}^{KBr} cm^{-1}: 1605 (CON<), UV λ_{max}^{EtOH} mμ (log ε): 315 (3.81), 334 (3.72). IIc: IR ν_{max}^{KBr} cm^{-1}: 1625 (CON<), UV λ_{max}^{EtOH} mμ (log ε): 314 (3.96).

Next the cyclization of 4-mercapto-5-chloro-3(2*H*)-pyridazinones (**4**—**6**) to the dipyridazo[4,5-*b*:4′,5′-*e*]-1,4-dithiin-diones was attempted to reveal that it was scarcely effected by heating in ethanol, but also smoothly attained when warmed the compounds, (**4**—**6**), with potassium carbonate in DMF for a short time to form the corresponding pairs of the compounds, the dipyridazo[4,5-*b*:4′,5′-*e*]-1,4-dithiin-1,6(2*H*,7*H*)-diones and the dipyridazo[4,5-*b*:4′,5′-*e*]-1,4-dithiin-1,9(2*H*,8*H*)-diones, such as Ia 28% in yield and IIa 42% in yield, Ib 40% in yield and IIb 40% in yield, and Ic 36% in yield and IIc 46% in yield.



Ia—c

IIa—c

4 : R=$PhCH_2$
5 : R=H
6 : R=Me

a : R=$PhCH_2$
b : R=H
c : R=Me

As the novel cyclization furnishes a concurrent formation of both compounds, the dipyridazo[4,5-*b*:4′,5′-*e*]-1,4-dithiin-1,6(2*H*,7*H*)-diones (Ia—c) and the dipyridazo[4,5-*b*:4′,5′-*e*]-1,4-dithiin-1,9(2*H*,8*H*)-diones (IIa—c), by starting from either 4-chloro-5-mercapto-3(2*H*)-pyridazinones (**1**—**3**) or 4-mercapto-5-chloro-3(2*H*)-pyridazinones (**4**—**6**) when kept in polar solvent by application of heat, but with somewhat different proportion in the both products, it might be reasonable to assume that during the course of the reaction, an intermediate holding C–S bond capable to be transformed, has probably to appear, provided there is non-existence of an equilibrium between the two products under such reaction conditions and being such the case. One of the most satisfactory intermediate for the requisite, is such keto-thioketo carbene species as $IIIa_1 \leftrightarrow IIIa_2 \leftrightarrow IIIa_3$ and $IIIb_1 \leftrightarrow IIIb_2$, which are generated by dehydrochlorination of **1**—**3** and **4**—**6** respectively and regenerated by a reversible interconversion through an activated intermediate state (IIIab) or the like, as Chart 1 shown below.

Subsequently the dipolar species, $IIIa_2$ or $IIIb_2$, dimerizes *per se* in 1,3-fashion to form the dipyridazo[4,5-*b*:4′,5′-*e*]-1,4-dithiin-1,6(2*H*,7*H*)-diones (Ia-c), whereas the species, $IIIa_2$

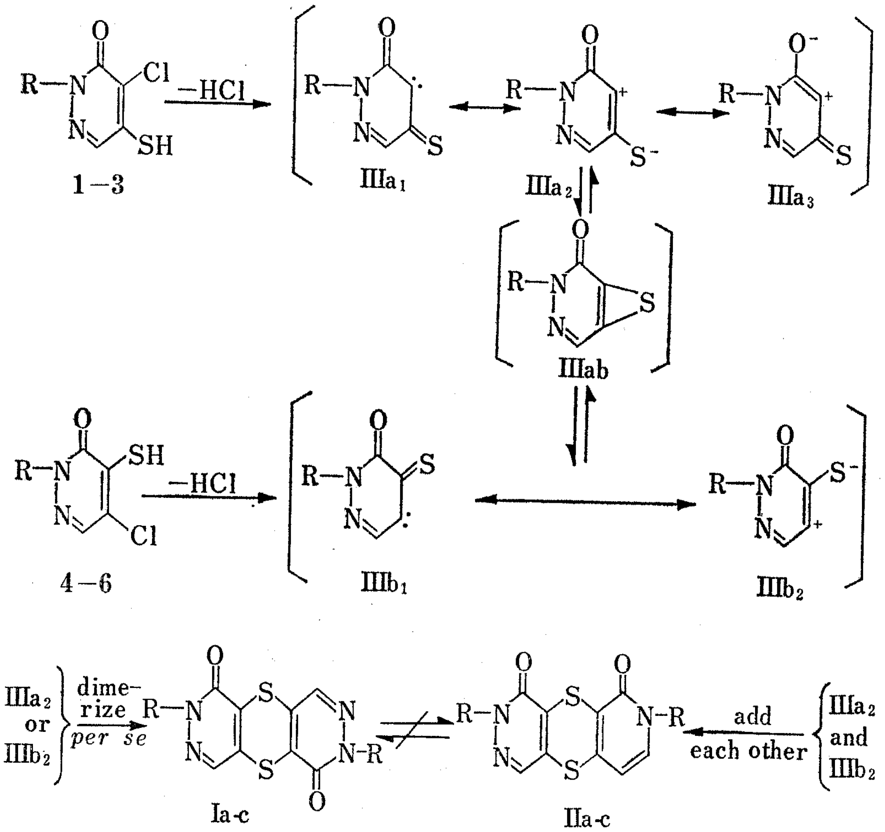
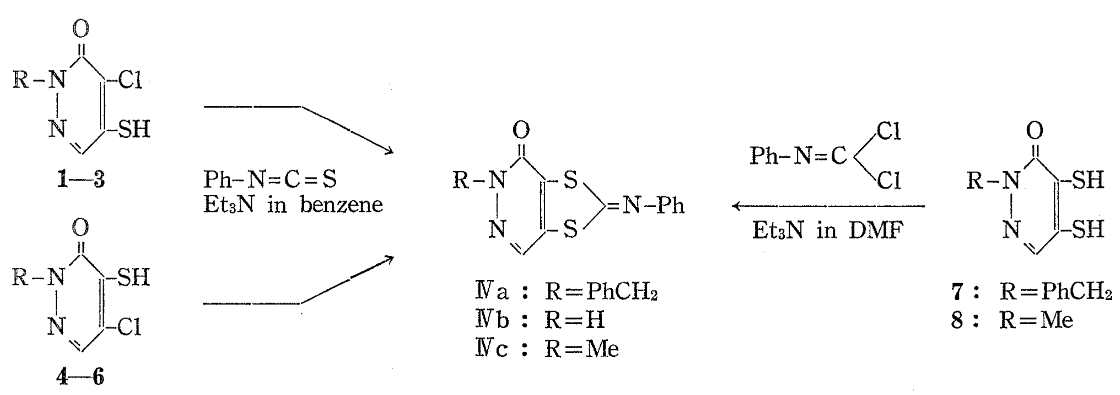


Chart 1

and $IIIb_2$, add mutually in the same fashion to give the dipyridazo[4,5-*b*:4′,5′-*e*]-1,4-dithiin-1,9(2*H*,8*H*)-diones (IIa-c).

The postulated active intermediates were caught though indirectly, according to the procedure described by R. Huisgen and his co-workers[9,10] and R. Selvarajan, *et al.*,[11] as 2-phenylimino-5-benzylpyridazo[4,5-*d*]-1,3-dithiol-4(5*H*)-one and the homologs, with rather poor yields, such as IVa 14% from **1** and 15% from **4**, (IVb) 8% from **2** and 6% from **5**, (IVc) 15% from **3** and 14% from **6**, along with the major products, mixtures of the corresponding dipyridazo[4,5-*b*:4′,5′-*e*]-1,4-dithiin-1,6-(2*H*,7*H*)diones (Ia-c) and -1,9(2*H*,8*H*)-diones (IIa-c), by warming 2-benzyl-4-chloro-5-mercapto-3(2*H*)-pyridazione (**1**) and the homologs (**2**,**3**) or the corresponding isomers (**4**—**6**) with phenylisothiocyanate in the presence of triethylamine in dry benzene. The same 1,3-dithiol derivatives, (IVa) and (IVc), was also formed by ano-



---

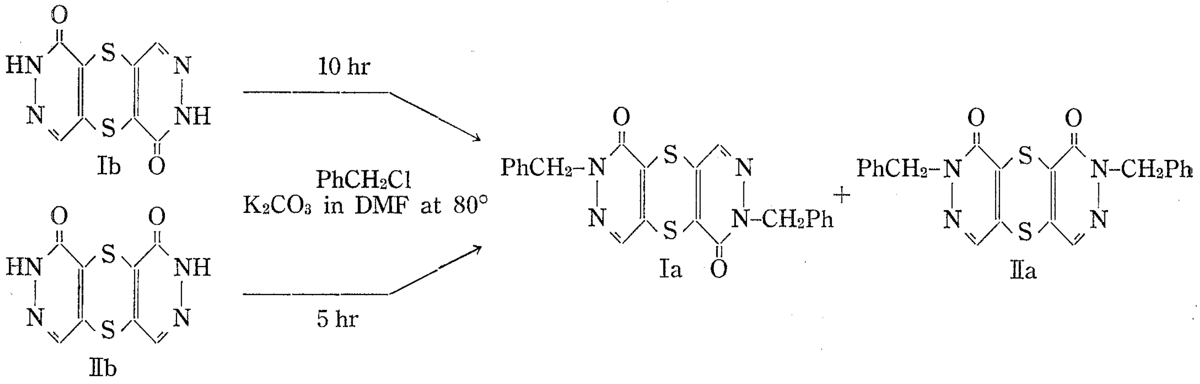
[9] R. Huisgen and V.W. Eberndröfer, *Experientia*, **17**, 566 (1961).

[10] R. Huisgen, H. König, G. Binsch and H.J. Sturm, *Angew. Chem.*, **73**, 368 (1961).

[11] R. Selvarajan, K. Narasimhan and S. Swaminathan, *Tetrahedron Letters*, **22**, 2089 (1967).

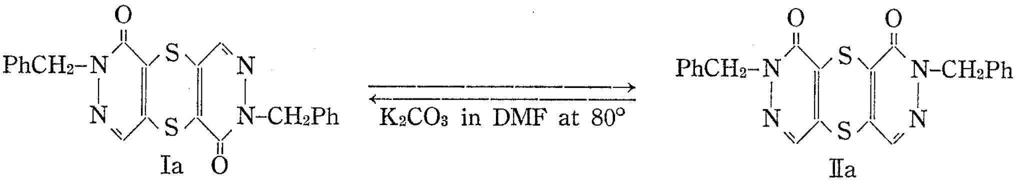
ther procedure in which 2-benzyl-4,5-dimercapto-3(2*H*)-pyridazinone (**7**) and 2-methyl-4,5-dimercapto-3(2*H*)-pyridazinone (**8**) was allowed to react with phenylcarbamyl dichloride in the presence of triethylamine in DMF in a rather good yield, such as IVa 57% in yield and IVc 54% in yield, respectively.

Non-existence of an equilibrium between the products, (Ia) and (IIa), during the course of the cyclization started from the reactant, **1** or **4**, briefly stated above, was thus observed that any of the compounds, Ia and IIa, was enough stable to exist without any contamination with any counterpart, IIa or Ia, when kept hot (—100°) in polar solvents, ethanol, ethylene glycol or DMF for several hours. However, the benzylation of Ib or IIb, by using benzylchloride in the presence of the potassium carbonate in DMF, with stirring at 80° for 10 hours or 5 hours respectively, produced a mixture of the two dibenzylated compounds, Ia and IIa, in each case, but with a different proportion in the products in yield percentage, such as Ia 58% in yield and IIa 6% in yield, or Ia 12% in yield and IIa 70% in yield, respectively.



The result suggests that there is a reversible interconversion or an equilibrium between the compounds, Ib and IIb or Ia and IIa, during the course of the benzylation.

In fact, treatment of Ia with potassium carbonate in DMF by warming at 80° for 10 hours realized a step, consisted of Ia 60% recovery and IIa 25% recovery, to an equilibrium and *vice versa*, another step, with Ia 25% recovery and IIa 37% recovery, to the equilibrium by starting from IIa, kept at 80° for 5 hours, while non-existence of such an equilibrium between Ib and IIb in the similar reaction condition was observed, experimentally. In this connection, it would be interresting to investigate a mechanism involved in the reversible interconversion.



Synthesis of 4-chloro-5-mercapto-3(2*H*)-pyridazinone (**1**—**3**), 4-mercapto-5-chloro-3(2*H*)-pyridazinone (**4**—**6**), 4,5-dimercapto-3(2*H*)-pyridazinone (**7**,**8**) and the related compounds was carried through an unambiguous route in the Chart 2 shown below.

2-Benzyl-4-chloro-5-mercapto-3(2*H*)-pyridazinone (**1**) or 2-methyl homolog (**3**) was easily obtained by mercaptylation of the corresponding 4,5-dichloro-3(2*H*)-pyridazinone (**1′**) or (**3′**) with ethanolic sodium hydrosulfide respectively, while 4-chloro-5-mercapto-3(2*H*)-pyridazinone (**2**) was prepared, without any contamination of the isomer, such as 4-mercapto-5-chloro-3(2*H*)-pyridazinone (**5**), by debenzylating (**1**), or 2-benzyl-4-chloro-5-benzylthio-3(2*H*)-pyridazinone (**9**) with aluminium chloride in warm toluene. Any of the 4-mercapto-5-chloro-3(2*H*)-pyridazinone (**4**—**6**) and 2-methyl-4,5-dimercapto-3(2*H*)-pyridazinone (**8**) were also prepared by debenzylation of the corresponding 4-benzylthio-5-chloro-3(2*H*)-pyridazinone (**15**) and

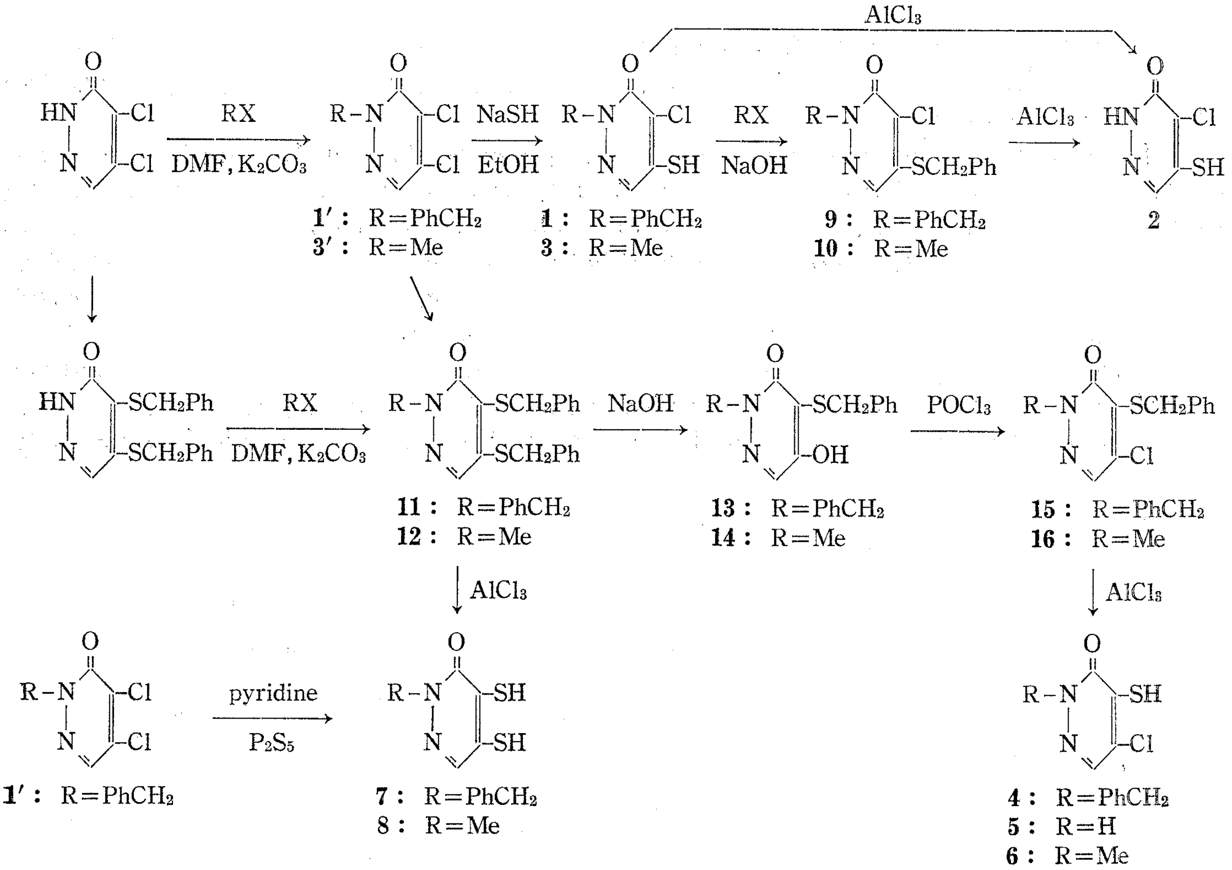


Chart 2

(**16**), or 2-methyl-4,5-bis(benzylthio)-3(2*H*)-pyridazinone (**12**), while 2-benzyl-4,5-dimercapto-3(2*H*)-pyridazinone (**7**) was derived by heating **1′** with phosphorus pentasulfide in dry-pyridine. 2-Benzyl-4,5-bis(benzylthio)-3(2*H*)-pyridazinone (**11**) was hydrolyzed with ethanolic sodium hydroxide to give predominatly 2-benzyl-4-benzylthio-5-hydroxy-3(2*H*)-pyridazinone (**13**) from which 2-benzyl-4-benzylthio-5-chloro-3(2*H*)-pyridazinone (**15**) was derivable by chlorination with phosphorus oxychloride. The structural assignment of the isomeric relation ship between **9** and **15** was ascertained by the fact that both compounds gave the same product (**11**), and (**9**) was obtained not only from **1**, but from 4-chloro-5-benzylthio-3(2*H*)-pyridazinone,[1] by benzylation.

2-Methyl related compounds were also prepared by analoguous method in that of benzyl homologs.

Experimental[12]

The Concurrent Formation of 2,7-Dibenzyldipyridazo[4,5-*b*:4′,5′-*e*]-1,4-dithiin-1,6(2*H*,7*H*)-dione (Ia) and 2,8-Dibenzyldipyridazo[4,5-*b*:4′,5′-*e*]-1,4-dithiin-1,9(2*H*,8*H*)-dione (IIa) from 2-Benzyl-4-chloro-5-mercapto-3(2*H*)-pyridazinone (1)——1 (0.5 g) was heated under reflux in ethanol (10 ml) for 10 hours. The reaction mixture was concentrated to dryness. The residue was extractd with dichloromethane. The dichloromethane sol. was washed with dil. sodium hydroxide sol., water and dried over anhyd. sodium sulfate. The residue obtained by concentration of dichloromethane, was chromatographed over silica-gel to give 0.2 g (57%) of Ia as yellowish orange needles (benzene), mp 265°. *Anal.* Calcd. for $C_{22}H_{16}O_2N_4S_2$: C, 61.09; H, 3.73; N, 12.95. Found: C, 61.20; H, 3.76; N, 12.68. and 0.05 g(14%) of IIa as reddish purple needles

---

[12] All melting points are uncorrected. IR spectra were taken on Hitachi EPI-S_2 recording spectrometer in potassium bromide discs. UV spectra were taken on Shimazu MPS-50 instrument in 95% EtOH. NMR spectra were taken on Japan Electron Optics Lab. C-60 spectrometer with tetramethylsilane (TMS) as an internal standard. Mass spectra were measured on Hitachi RMU-6 spectrometer.

(benzene), mp 263°. *Anal.* Calcd. for $C_{22}H_{16}O_2N_4S_2$: C, 61.09; H, 3.73; N, 12.95. Found: C, 61.33; H, 3.96; N, 12.91.

The Concurrent Formation of Dipyridazo[4,5-*b*:4′,5′-*e*]-1,4-dithiin-1,6(2*H*,7*H*)-dione (Ib) and Dipyridazo-[4,5-*b*:4′,5′-*e*]-1,4-dithiin-1,9(2*H*,8*H*)-dione (IIb) from 4-Chloro-5-mercapto-3(2*H*)-pyridazinone (2)——2 (3.2 g) was heated under reflux in ethanol (100 ml) for 3 hours.

The reaction mixture was concentrated to almost dryness. The residual solid was collected, washed with water, and extracted with aq. ethanol (1:5) by using a Soxley-extracter for 48 hours.

A pale reddish orange solid was separated from a yellow solution.

The solid was collected, washed with ethanol and dried, which yielded 1.4 g (58%) of Ib, mp>300°. IR ν_{max}^{KBr} cm^{-1}: 3100—2870 (HN<, broad). 1605 (CON<). UV λ_{max}^{EtOH} mμ: 310, 328 (saturated solution). *Anal.* Calcd. for $C_8H_4O_2N_4S_2$: C, 38.13; H, 1.60; N, 22.23. Found: C, 38.51; H, 1.85; N, 22.28.

On the other hand, the aq. ethanolic sol. was concentrated to dryness *in vacuo* to give a yellow solid (IIb′) (mono-hydrate of IIb, mp>300°, which was easily dehydrated by heating in abs. ethanol to unhydrous 0.5 g (20%) of IIb as red needles, mp>300°. IIb′: IR ν_{max}^{KBr} cm^{-1}: 3200—2750 (HN<, broad), 1640, 1615 (CON<, doublet). UV λ_{max}^{EtOH} mμ: 309 (saturated solution). *Anal.* Calcd. for $C_8H_6O_3N_4S_2$: C, 35.59; H, 2.24; N, 20.75. Found: C, 35.82; H, 1.93; N, 20.88. IIb: IR ν_{max}^{KBr} cm^{-1}: 3200—2800 (HN<, broad), 1615 (CON<). UV λ_{max}^{EtOH} mμ: 309 (saturated solution). *Anal.* Calcd. for $C_8H_4O_2N_4S_2$: C, 38.13; H, 1.60; N, 22.23. Found: C, 38.60; H, 1.97; N, 22.47.

The Concurrent Formation of 2,7-Dimethyldipyridazo[4,5-*b*:4′,5′-*e*]-1,4-dithiin-1,6(2*H*,7*H*)-dione (Ic) and 2,8-Dimethyldipyridazo[4,5-*b*:4′,5′-*e*]-1,4dithiin-1,9(2*H*,8*H*)-dione (IIc) from 2-Methyl-4-chloro-5-mercapto-3(2*H*)-pyridazinone (3)——3 (0.5 g) was warmed in DMF (5 ml) for 1 hour. The reaction mixture was poured into water.

Precipitated solid was extracted with dichloromethane. The dichloromethane sol. was washed with water, dried over anhyd. sodium sulfate and chromatographed over silica gel to give 0.17 g (40%) of Ic as reddish purple needles, mp>300°. *Anal.* Calcd. for $C_{10}H_8O_2N_4S_2$: C, 42.89; H, 2.88; N, 20.01. Found: C, 43.12; H, 3.04; N, 20.13. and 0.1 g (24%) of IIc as yellow needles, mp>300°. *Anal.* Calcd. for $C_{10}H_8O_2N_4S_2$: C, 42.89; H, 2.88; N, 20.01. Found: C, 43.13; H, 3.12; N, 20.05.

The Concurrent Formation of Ia and IIa from 2-Benzyl-4-mercapto-5-chloro-3(2*H*)-pyridazinone (4)——4 (0.25 g) was warmed in DMF (5 ml) in the presence of potassium carbonate (0.4 g) for 30 minutes. After concentration of the reaction mixture *in vacuo*, the residue was extracted with dichloromethane. The dichloromethane sol. was washed with water, dried over anhyd. sodium sulfate and chromatographed over silica gel to give 0.06 g (30%) of Ia and 0.09 g (45%) of IIa. These compounds were identical with Ia and IIa, obtained from 1, respectively by mixed melting point, comparison of their IR spectra and their *Rf* of TLC.

The Concurrent Formation of Ib and IIb from 4-Mercapto-5-chloro-3(2*H*)-pyridazinone (5)——5 (0.3 g) was warmed in DMF (5 ml) in the presence of potassium carbonate (1.4 g) for 1 hour. The reaction mixture was poured into water (20 ml). Precipitated pale reddish orange solid was collected, washed with water and dried to give 0.1 g (40%) of Ib. On the other hand, IIb′ obtained from the filtrate by acidification with concd. hydrochloric acid, was dehydrated to give 0.1 g (40%) of IIb. These compounds were identical with Ib and IIb obtained from 2, respectively, by comparison of their IR and UV spectra.

The Concurrent Formation of Ic and IIc from 2-Methyl-4-mercapto-5-chloro-3(*H*)2-pyridazinone (6)——6 (0.35 g) was warmed in DMF (5 ml) in the presence of potassium carbonate (1.4 g) for 30 minutes. After concentration of the reaction mixture *in vacuo*, the residue was extracted with dichloromethane. The dichloromethane sol. was washed with water, dried over anhyd. sodium sulfate and chromatographed over silica gel to give 0.10 g (36%) of Ic and 0.13 g (46%) of IIc. These compounds were identical with Ic and IIc, obtained from 3 by comparison of their IR and UV spectra and their *Rf* of TLC, respectively.

Formation of Ib by Debenzylation of Ia——To a solution of anhyd. aluminium chloride (0.3 g) in dry-toluene (15 ml) was added Ia (0.2 g) rapidly with stirring and the whole was kept at 60° for 5 hours. On cooling, to the reaction mixture was added water. Precipitated solid was collected and washed with water. The crude product was dissolved in dil. sodium hydroxide sol. and filtered. The filtrate was acidified with concd. hydrochloric acid to give 0.1 g (75%) of Ib. This compound was identical with an authentic sample by comparison of IR and UV spectra.

Formation of IIb by Debenzylation of IIa——IIa (0.2 g) was allowed to react similarly as described above to give 0.1 g (74%) of IIb′ as mono hydrate of IIb. This compound was identical with an authentic sample by comparison of IR and UV spectra.

2-Phenylimino-5-benzylpyridazo[4,5-*d*]-1,3-dithiol-4(5*H*)-one (IVa)——a) From 1: (1) (0.5 g) was heated under reflux with phenylisothiocyanate in the presence of triethylamine (0.2 g) in dry-benzene (5 ml) for 2 hours. The reaction mixture was concentrated to dryness *in vacuo*. The residue was extracted with dichloromethane. The dichloromethane sol. was washed with dil. sodium hydroxide sol., water and dried over anhyd. sodium sulfate. The residue obtained by concentration of dichloromethane, was chromatographed over silica gel to give 0.1 g (14%) of IVa as colorless needles (EtOH), mp 145°. *Anal.* Calcd. for $C_{18}H_{13}ON_3S_2$: C, 61.50; H, 3.73; N, 11.96. Found: C, 61.74; H, 3.99; N, 11.67.

b) From **4**: 0.07 g (15%) of (IVa) was also obtained by treating **4** (0.25 g) in a similar manner as described above.

2-Phenyliminopyridazo[4,5-*d*]-1,3-dithiol-4(5*H*)-one (IVb)——a) From **2**: A treatment of **2** (1.6 g) as described above gave 0.2 g (8%) of IVb as colorless needles, mp 204°. *Anal.* Calcd. for $C_{11}H_7ON_3S_2$: C, 50.23; H, 2.68; N, 15.98. Found: C, 50.44; H, 2.87; N, 15.89.

b) From **5**: 0.08 g (6%) of IVb was also obtained by treating **5** (0.81 g) in a similar manner as described above.

2-Phenylimino-5-methylpyridazo[4,5-*d*]-1,3-dithiol-4(5*H*)-one (IVc)——a) From **3**: A treatment of **3** (0.9 g) as described above gave 0.2 g (15%) of IVc as colorless plates, mp 198°. *Anal.* Calcd. for $C_{12}H_9$-
above.
ON_3S_2: C, 52.41; H, 3.30; N, 15.28. Found: C, 52.40; H, 3.33; N, 15.23.

b) From **6**: 0.18 g (14%) of IVc was also obtained by treating **6** (0.45 g) in a similar manner as described above.

IVa from 2-Benzyl-4,5-dimercapto-3(2*H*)-pyridazinone (7)——To a solution of **7** (0.25 g) in DMF (2 ml) was added phenylcarbamyl dichloride (0.34 g) and triethylamine (0.2 g) and the whole was warmed on a steam-bath for 10 minutes. The reaction mixture was poured into water and extracted with dichloromethane. The dichloromethane sol. was washed with dil. sodium hydroxide sol., water and dried over anhyd. sodium sulfate. The residue obtained by concentration of dichloromethane, was chromatographed over silica gel to give 0.2 g (57%) of IVa. This compound was identical with an authentic sample in all respects.

IVc from 2-Methyl-4,5-dimercapto-3(2*H*)-pyridazinone (8)——**8** (0.34 g) was allowed to react with phenylcarbamyl dichloride (0.35 g) in a similar manner as described above to give 0.3 g (54%) of IVc. This compound was identical with an authentic sample in all respects.

The Benzylation of Ib——To a mixture of benzylchloride (0.6 g) and potassium carbonate (0.8 g) in DMF (20 ml) was added (Ib) and the whole was stirred at 80° for 10 hours. The reaction mixture was concentrated to dryness *in vacuo*. The residual solid was extracted with dichloromethane. The dichloromethane sol. was washed with water and drided over anhyd. sodium sulfate, which produced two spots on TLC. Therefore, the residue obtained by concentration of dichloromethane, was chromatographed over silica gel to give 0.5 g (58%) of Ia (benzene) and 0.05 g(6%) of IIa (benzene). These compounds were identical with the corresponding authentic sample in all respects.

The Benzylation of IIb——IIb (0.5 g) was benzylated similarly as described above to give 0.1 g (12%) of Ia and 0.6 g (70%) of IIa. These compounds were identical with the corresponding authentic sample in all respects.

The Reversible Interconversion of Ia and IIa——a) From Ia: Ia (0.43 g) was allowed to stirr at 80° with potassium carbonate (0.4 g) in DMF (10 ml) for 10 hours. The reaction mixture was treated similarly as described for the benzylation of Ib to give 0.25 g(60%) of Ia and 0.10 g (25%) of IIa.

b) From IIa: IIa (0.43 g) was allowed to stirr at 80° with potassium carbonate (0.4 g) in DMF (10 ml) for 5 hours. The reaction mixture was treated similarly as described above to give 0.1 g (25%) of Ia and 0.15 g (37%) of IIa. These compounds were identical with the corresponding authentic sample in all respects.

2-Benzyl-4,5-dichloro-3(2*H*)-pyridazinone (1′)——To a mixture of benzylchloride (3.1 g) and potassium carbonate (13.8 g) in DMF (20 ml) was added 4,5-dichloro-3(2*H*)-pyridazinone (3.3 g) and the whole was stirred at room temperature for 1 hour. The reaction mixture was poured into water and kept them at room temperature. Precipitated solid was collected and extracted with hot ethanol. The ethanol sol. was concentrated to give 2.7 g (54%) of **1′** as colorless crystals, mp 89° (mp 87—89° in the literature[8]).

2-Methyl-4,5-dichloro-3(2*H*)-pyridazinone (3′)——4,5-Dichloro-3(2*H*)-pyridazinone (3.3 g) was allowed to react with methyl iodide (3.4 g) in a similar manner as described above to give 2.9 g (80%) of **3′** as colorless needles, (petroleum ether), mp 91° (mp 90—91° in the literature[13]).

2-Benzyl-4-chloro-5-mercapto-3(2*H*)-pyridazinone (1)——To a solution of 35% aq. sodium hydrosulfide (1.4 g) in ethanol (15 ml) was added (1′) (1.0 g) and the whole was stirred at room temperature for 2 hours. The reaction mixture was concentrated to almost dryness *in vacuo*. To the residue was added water. The aq. solution was acidified with concd. hydrochloric acid to precipitate a yellow solid which was collected, washed with a small amount of water and dissolved in dil. sodium hydroxide sol. to remove an insoluble solid. The aq. alkaline sol. was acidified with concd. hydrochloric acid to pH=1. Deposited solid was collected, washed with water and recrystallized from benzene and cyclohexane to give 0.5 g (50%) of **1**, as colorless needles, mp 165°. IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 2400 (SH), 1610 (CON<). *Anal.* Calcd. for $C_{11}H_9ON_2SCl$: C, 52.42; H, 3.60; N, 11.12. Found: C, 52.31; H, 3.87; N, 11.29.

2-Methyl-4-chloro-5-mercapto-3(2*H*)-pyridazinone (3)——**1′** (3.6 g) was allowed to react with aq. 35% sodium hydrosulfide sol. (9.6 g) in ethanol (100 ml) as described above. 2.0 g (58%) of **3** was obtained, as colorless needles, mp 179°. IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 2380 (SH), 1605 (CON<). *Anal.* Calcd. for $C_5H_5ON_2SCl$: C, 34.02; H, 2.86; N, 15.88. Found: C, 33.98; H, 3.15; N, 15.71.

---

[13] R.F. Homer, H. Gregory and L.F. Wiggins, *J. Chem. Soc.*, **1948, 2191.**

4-Chloro-5-mercapto-3(2*H*)-pyridazinone (2)——1 (2.5 g) was debenzylated by allowing to react with anhyd. aluminium chloride (2.9 g) in dry-toluene (50 ml) in a similar manner as described before to give 1.2 g (75%) of **2** as pale yellow needles, mp>300°. IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1}: 3200—2750 (HN<, broad), 2480 (SH), 1630 (CON<). *Anal.* Calcd. for $C_4H_3ON_2SCl$: C, 29.54; H, 1.86; N, 17.23. Found: C, 29.84; H, 1.93; N, 17.41.

2-Benyl-4-chloro-5-benzylthio-3(2*H*)-pyridazinone (9)——Benzylchloride (1.4 g) was added to the sodium thiolate solution, containing **1** (2.5 g) in a mixture of 5% sodium hydroxide sol. (8 ml) and ethanol (8 ml) and the whole was stirred at room temperature for 1 hour. Precipitated solid was collected, washed with water and recrystallized from ethanol to 3.0 g (80.8%) of **9** as colorless needles, mp 175°. *Anal.* Calcd. for $C_{18}H_{15}ON_2SCl$: C, 63.06; H, 4.41; N, 8.17. Found: C, 63.15; H, 4.48; N, 8.25.

2-Methyl-4-chloro-5-benzylthio-3(2*H*)-pyridazinone (10)——**3** was allowed to react with benzylchloride (0.8 g) similarly as described above to 1.1 g (84.7%) of **10** as colorless crystals (petroleum ether), mp 110°. *Anal.* Calcd. for $C_{12}H_{11}ON_2SCl$: C, 54.02; H, 4.16; N, 10.50. Found: C, 54.11; H, 4.20; N, 10.62.

2-Benzyl-4,5-bis(benzylthio)-3(2*H*)-pyridazinone (11)——To a mixture of benzylchloride (7.7 g) and potassium carbonate (24 g) in DMF (100 ml) was added 4,5-bis(benzylthio)-3(2*H*)-pyridazinone (17 g) and the whole was stirred at room temperature for 2 hours.

The reaction mixture was concentrated to dryness *in vacuo*. To the residue was added water. Precipitated solid was collected, washed with water and recrystallized from ethanol to give 15.7 g (73.0%) of **11** as pale green needles, mp 92°. *Anal.* Calcd. for $C_{25}H_{22}ON_2S_2$: C, 69.83; H, 5.16; N, 6.52. Found: C, 69.63; H, 5.43; N, 6.25.

2-Methyl-4,5-bis(benzylthio)-3(2*H*)-pyridazinone (12)——4,5-Bis(benzylthio)-3(2*H*)-pyridazinone (8.5 g) was allowed to react with methyl iodide (5.6 g) in a similar manner as described above to obtain 7.2 g (81.8%) of **12** as colorless needles, mp 91°. *Anal.* Calcd. for $C_{19}H_{18}ON_2S_2$: C, 64.46; H, 5.13; N, 7.91. Found: C, 64.49; H, 5.10; N, 7.78.

2-Benzyl-4-benzylthio-5-hydroxy-3(2*H*)-pyridazinone (13)——**11** (8.6 g) was heated under reflux with aq. 20% sodium hydroxide solution (40 ml) in ethanol (200 ml) for 3 hours. The reaction mixture was concentrated to almost dryness *in vacuo*. The residue was diluted with water and filtered. The filtrate was acidified with concd. hydrochloric acid to precipitate a solid, which was collected, washed with water and fractionally recrystallized from benzene and cyclohexane to 4.4 g (68.8%) of **13** as colorless small needles, mp 150°. *Anal.* Calcd. for $C_{18}H_{16}O_2N_2S$: C, 66.73; H, 4.98; N, 8.65. Found: C, 66.77; H, 5.19; N, 8.47. Then, the mother liquor was concentrated to dryness *in vacuo*. The residual solid was recrystallized from ethanol to give 0.5 g (7.7%) of 4-hydroxy-5-benzylthio-2-benzyl-3(2*H*)-pyridazinone as colorless needles, mp 142°. *Anal.* Calcd. for $C_{18}H_{16}O_2N_2S$: C, 66.73; H, 4.98; N, 8.65. Found: C, 66.90; H, 5.24; N, 8.77.

2-Methyl-4-benzylthio-5-hydroxy-3(2*H*)-pyridazinone (14)——**12** (5.2 g) was allowed to react with aq. 20% sodium hydroxide solution (30 ml) in ethanol (150 ml) similarly as described above to obtain 2.0 g (54%) of **14** as colorless plates, mp 167°. *Anal.* Calcd. for $C_{12}H_{11}O_2N_2S$: C, 58.11; H, 4.88; N, 11.30. Found: C, 58.30; H, 5.16; N, 11.27.

2-Benzyl-4-benzylthio-5-chloro-3(2*H*)-pyridazinone (15)——**13** (1.6 g) was warmed with phosphorus oxychloride (10 ml) on a steam bath for 3 hours. The reaction mixture was poured onto crushed ice. Precipitated solid was extracted with chloroform. The chloroform sol. was washed with dil. sodium hydroxide sol., water and dried over anhyd. sodium sulfate. The residue obtained by concentration of chloroform, was recrystallized from petroleum ether to give 0.8 g (50.0%) of **15** as yellow crystals, mp 96°. *Anal.* Calcd. for $C_{18}H_{15}ON_2SCl$: C, 63.21; H, 4.42; N, 8.19. Found: C, 63.17; H, 4.56; N, 8.04.

2-Methyl-4-benzylthio-5-chloro-3(2*H*)-pyridazinone (16)——**14** (4.5 g) was chlorinated in a similar manner as described above to obtain 3.1 g (68.7%) of **16** as yellow oil, bp 186° (4 mmHg). *Anal.* Calcd. for $C_{12}H_{11}ON_2SCl$: C, 54.02; H, 4.16; N, 10.50. Found: C, 54.16; H, 4.17; N, 10.46.

2-Benzyl-4-mercapto-5-chloro-3(2*H*)-pyridazinone (4)——To a solution of anhyd. aluminium chloride (0.7 g) in dry-toluene (30 ml) was added **15** (1.7 g), rapidly with stirring and the whole was kept at 80° for 3 hours. On cooling, to the reaction mixture was added water. The aq. acidific sol. was extracted fully with benzene. The benzene sol., combined with the toluene sol., was treated with dil. sodium hydroxide sol. The aq. alkaline sol. was acidified with concd. hydrochloric acid to pH=3, extracted with dichloromethane and dried over anhyd. sodium sulfate. The residue obtained by concentration of dichloromethane, was distilled to give 0.5 g (40%) of **4** as pale yellow solid, bp 110° (3 mmHg) (mp 61—62°). IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1}: 2500 (SH), 1625 (CON<). *Anal.* Calcd. for $C_{11}H_9ON_2SCl$: C, 52.42; H, 3.60; N, 11.12. Found: C, 52.16; H, 3.49; N, 11.51.

4-Mercapto-5-chloro-3(2*H*)-pyridazinone (5)——**15** (1.7 g) was allowed to react with anhyd. aluminium chloride (1.5 g) in dry-toluene (30 ml) at 60° for 6 hours. On cooling, to the reaction mixture was added water. Precipitated solid was collected, washed with water and recrystallized from ethanol to give 0.5 g (65.8%) of **5** as yellowish green needles, mp 157°. IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1}: 3100—2780 (HN<, broad), 2450 (SH), 1630 (CON<). *Anal.* Calcd. for $C_4H_3ON_2SCl$: C, 29.65; H, 1.87; N, 17.29. Found: C, 29.57; H, 2.03; N, 17.52.

2-Methyl-4-mercapto-5-chloro-3(2*H*)-pyridazinone (6)——**16** (2.6 g) was allowed to react with anhyd. aluminium chloride (2.9 g) similarly as described above to give 1.1 g (64.7%) of **6** as pale yellow needles, mp 85°. IR ν_{max}^{KBr} cm^{-1}: 2500 (SH), 1610 (CON<). *Anal.* Calcd. for $C_5H_5ON_2SCl$: C, 34.02; H, 2.86; N, 15.88. Found: C, 34.28; H, 2.95; N, 15.92.

2-Benzyl-4,5-dimercapto-3(2*H*)-pyridazinone (7)——1′ (2.5 g) was heated under gentle reflux with powdered phosphorus pentasulfide (13.3 g) in dry-pyridine (80 ml) for 5 hours. An excess pyridine was removed *in vacuo*. To the residue was added water and the resulting suspension was digested on a steam bath until an evolution of hydrosulfide had ceased. Then, the solution was made alkaline by dil. sodium hydroxide sol., washed with ether and filtered. The filtrate was acidified with concd. hydrochloric acid to precipitate a solid, which was collected, washed with water, dried and recrystallized from benzene and cyclohexane to give 1.2 g (50.0%) of **7** as yellow needles, mp 97°. IR ν_{max}^{KBr} cm^{-1}: 2430 (SH), 1655—1555 (CON<, broad). *Anal.* Calcd. for $C_{11}H_{10}ON_2S_2$: C, 52.84; H, 4.03; N, 11.21. Found: C, 53.01; H, 4.17; N, 11.07.

2-Methyl-4,5-dimercapto-3(2*H*)-pyridazinone (8)——12 (3.5 g) was allowed to react with anhyd. aluminium chloride (2.9 g) in dry-toluene (50 ml) at 60° for 6 hours. On cooling, to the reaction mixture was added water. Precipitated solid was collected, washed with water, dried and recrystallized from benzene and cyclohexane to give 1.0 g (59.0%) of **8** as pale green needles, mp 112°. IR ν_{max}^{KBr} cm^{-1}: 2430, 2350 (SH), 1595 (CON<). *Anal.* Calcd. for $C_5H_6ON_2S_2$: C, 34.90; H, 3.52; N, 16.27. Found: C, 35.11; H, 3.73; N, 16.43.

Acknowledgement The authors are grateful to Dr. J. Iwao, Mr. Yamazaki, Dr. K. Abe, Dr. T. Okuda and Dr. K. Kodera of Tanabe Pharmaceutical Co., Ltd. for NMR spectra measurement and screening tests, and to Dr. S. Yoshina and Dr. A. Tatematsu of Faculty of Pharmaceutical Sciences, Meizyo University for Mass spectral data, and to Dr. W. Nagata and Dr. H. Watanabe of Shionogi Pharmaceutical Co., Ltd. for the measurement of dipole moment. Elemental analgses were carried out by Mrs. T. Kataoka to whom the authors' thanks are due. Thanks are also given to M. Ban and Y. Ogiso for their assistances in the experimental work.