Synthesis of Pyridazine Derivatives with Sulfur-Containing Substituent. III.¹⁾
Two Types of Cyclizations in the Concurrent Formation of 1,6-
and 1,9-Disubstituteddipyridazo[4,5-*b*:4',5'-*e*]-
1,4-dithiin Derivatives. (2)

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4,5-Dimercapto-3(2*H*)-pyridazinones (7,8,9), 3,4-dichloropyridazine-5-thiol (11), which must have been produced during the debenzylolation reaction of 3,4-dichloro-5-benzylthio-pyridazine (10), and 4-chloro-5-mercapto-3(2*H*)-pyridazinethiones (13,14) furnished the concurrent formation of the corresponding pairs of dipyridazo[4,5-*b*:4',5'-*e*]-1,4-dithiin derivatives, respectively.

On the other hand, 3-methylthio- (15) and 3-morpholino-4-chloropyridazine-5-thiol (16) formed the corresponding 1,6-disubstituted dipyridazo[4,5-*b*:4',5'-*e*]-1,4-dithiin alone, however, 3-methylthio- (17) and 3-morpholinopyridazine-4,5-dithiol (18) concurrently formed the corresponding pairs of 1,6- and 1,9-disubstituted derivatives.

For the interpretation of these reactions, the formation mode was proposed to be divided in two classes according to the characters of the thioketo carbene species as active intermediates. The former reactions proceed through the corresponding thioketo carbene species which is so reversibly interconvertible, that subsequently dimerizes *per se* in 1,3-dipolar fashion to concurrently form a pair of the corresponding derivatives. The latter reactions also proceed through the relevant thioketo carbene species in the same fashion of dimerization as described in the former reactions, however, existence of any reversible interconversion between the counterpart one is scarcely inferred. So the relevant carbene species of the cyclization started with 15 and 16, independently exist as a pair in a definite mixing proportion, subsequently they combine by the two dimerization mode.

In the preceding paper¹⁾ of this series, attention has been drawn to the novel cyclization, through which 2,7-dibenzylidipyridazo[4,5-*b*:4',5'-*e*]-1,4-dithiin-1,6(2*H*,7*H*)-dione (Ia) and 2,8-dibenzylidipyridazo[4,5-*b*:4',5'-*e*]-1,4-dithiin-1,9 (2*H*,8*H*)-dione (IIa) concurrently forms, not only by heating 2-benzyl-4-chloro-5-mercapto-3(2*H*)-pyridazinone (1) in ethanol, but by warming 2-benzyl-4-mercapto-5-chloro-3(2*H*)-pyridazinone (4) in dimethylformamide (DMF)

1) Part II: K. Kaji, M. Kuzuya and R.N. Castle, *Chem. Pharm. Bull.* (Tokyo), 18, 147 (1970).

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in the presence of anhydrous potassium carbonate. For the interpretation of the reaction and analogous ones started with 2-unsubstituted- (2) and 2-methyl-4-chloro-5-mercapto-3(2*H*)-pyridazinone (3), or 2-unsubstituted- (5) and 2-methyl-4-mercapto-5-chloro-3(2*H*)-pyridazinone (6), the keto-thioketo carbenes as active intermediate species and a reversible interconversion among them have been also suggested, based on the experimental facts, absence of an equilibrium between the two products, (Ia) and (IIa), under the reaction condition, and trapping the intermediate species as 2-phenylimino-5-benzylpyridazo[4,5-*d*]-1,3-dithiol-4(5*H*)-one along with the major products, (Ia) and (IIa), by warming (1) or (4) with phenylisothiocyanate in the presence of triethylamine in dry benzene.

The present work deals with an extension of the concurrent formation of 1,6- and 1,9-disubstituted dipyridazo[4,5-*b*:4',5'-*e*]-1,4-dithiin derivatives to several reactions in which participate 4,5-dimercapto-3(2*H*)-pyridazinones (7)¹, (8), (9)¹, 3,4-dichloro-pyridazine-5-thiol (11), 4,5-disubstituted-3(2*H*)-pyridazinethiones (12–14), and 3-substituted-4,5-dimercaptopyridazines (17,18), with a discussion on two types of the cyclizations, classified by the characters of the active intermediate species involved in them.

2-Benzyl-4,5-dimercapto-3(2*H*)-pyridazinone (7) was heated in ethanol under reflux for 5 hours to form concurrently, with evolution of hydrogen sulfide, 2,7-dibenzylidipyridazo[4,5-*b*:4',5'-*e*]-1,4-dithiin-1,6(2*H*,7*H*)-dione (Ia) (36% in yield) and 2,8-dibenzylidipyridazo[4,5-*b*:4',5'-*e*]-1,4-dithiin-1,9(2*H*,8*H*)-dione (IIa) (18% in yield), similarly as started from (1). The concurrent formation of dipyridazo[4,5-*b*:4',5'-*e*]-1,4-dithiin-1,6(2*H*,7*H*)-dione (Ib) (40% in yield) and dipyridazo[4,5-*b*:4',5'-*e*]-1,4-dithiin-1,9(2*H*,8*H*)-dione (IIb) (16% in yield), or 2,7-dimethyldipyridazo[4,5-*b*:4',5'-*e*]-1,4-dithiin-1,6(2*H*,7*H*)-dione (Ic) (38% in yield) and 2,8-dimethyldipyridazo[4,5-*b*:4',5'-*e*]-1,4-dithiin-1,9(2*H*,8*H*)-dione (IIc) (24% in yield), was similarly performed by starting with 4,5-dimercapto-3(2*H*)-pyridazinone (8) or 2-methyl-4,5-dimercapto-3(2*H*)-pyridazinone (9), respectively.

With a view to examining the possibility for the cyclization of 3,4-dichloropyridazine-5-thiol (11), debenzylation of 3,4-dichloro-5-benzylthiopyridazine (10) by a general procedure using aluminium chloride in dry toluene with stirring, was attempted to carry for the preparation of the former compound (11). Unexpectedly, the reaction seemed rather difficult to be regulated to stop at the debenzylation stage, but through which it readily underwent the cyclization. The resulted products were chromatographed over silica gel to separate into

1,6-dichlorodipyridazo[4,5-*b*:4',5'-*e*]-1,4-dithiin (Id)³⁾ (mp 286°, (decomp.), pale green needles, 31% in yield) and 1,9-dichlorodipyridazo[4,5-*b*:4',5'-*e*]-1,4-dithiin (IIId) (mp 239° (decomp.), pale yellow needles, 14% in yield), as each of these compounds proved to be identical by mixed melting point test, comparison of the infrared (IR) and ultraviolet (UV) spectra and the *R_f* values in TLC, with the corresponding one of the dichloro compounds derived from Ib and IIb, by chlorination with phosphorus oxychloride in the presence of dimethylaniline.

An extension of the cyclization to the synthesis of dipyridazo[4,5-*b*:4',5'-*e*]-1,4-dithiin-1,6(2*H*,7*H*)-dithione (Ie), dipyridazo[4,5-*b*:4',5'-*e*]-1,4-dithiin-1,9(2*H*,8*H*)-dithione (IIe), and their derivatives or the related compounds, was attempted to carry as described below.

4-Chloro-5-mercapto-3(2*H*)-pyridazinethione (**12**) was heated in ethanol under reflux for 5 hours. The crude products mixture was directly benzylated with benzylchloride, prior to further purification, as the separation of the products, (Ie) and (IIe), from their mixture was rather difficult. Separation of the benzylated derivatives was effected by chromatography over silica gel to give a pair of the compounds, 1,6-bis(benzylthio)dipyridazo[4,5-*b*:4',5'-*e*]-1,4-dithiin (If)³⁾ (mp 178°, yellow needles, 50% in yield) and 1,9-bis(benzylthio)dipyridazo[4,5-*b*:4',5'-*e*]-1,4-dithiin (IIIf) (mp 170°, colorless needles, 24% in yield). Individual formation of dipyridazo[4,5-*b*:4',5'-*e*]-1,4-dithiin-1,6(2*H*,7*H*)-dithione (Ie) (mp >300°) or dipyridazo[4,5-*b*:4',5'-*e*]-1,4-dithiin-1,9(2*H*,8*H*)-dithione (IIe) (mp >300°), though difficult to separate each one of them from the mixture as described above, was easily carried by mercaptylation of Id or IIId respectively, in addition, reversely each of the latter, Id or IIId was readily recovered by chlorination of the corresponding one of the former Ie or IIe. The structural proofs of a pair of the compounds, (If) and (IIIf), were made on the basis of the following facts — the each product, (Ie) or (IIe) was individually recovered from the corresponding one of the derivatives, (If) and (IIIf), and in NMR spectra (in CDCl₃), despite the capabilities of Ie and IIe to form the ambident anion, the two derivatives exhibited the value, (If): 5.33(4H, singlet, S-CH₂-), 1.15(2H, singlet, ring-H) and (IIIf): 5.36 (4H, singlet, S-CH₂-), 1.21(2H, singlet, ring-H).

A similar result, concurrent formation of Ie and IIe, which were also identified as a pair of If (24% in yield) and IIIf (22% in yield), was observed in the case started with 4,5-dimercapto-3(2*H*)-pyridazinethione (**13**).³⁾ Furthermore, 2-methyl-4,5-dimercapto-3(2*H*)-

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

pyridazinethione (**14**) was warmed at 80° in DMF for 1 hour, through chromatographic separation of the products, to form also a couple of 2,7-dimethyldipyridazo[4,5-*b*:4',5'-*e*]-1,4-dithiin-1,6(2*H*,7*H*)-dithione (Ig) (mp >300°, red needles, 44% in yield) and 2,8-dimethyldipyridazo[4,5-*b*:4',5'-*e*]-1,4-dithiin-1,9(2*H*,8*H*)-dithione (IIg) (mp >300°, yellow needles, 25% in yield). Structural assignment of the two products (Ig) and (IIg), was based on the comparison of each of their UV spectra with that of the corresponding one of the compounds, (Ie) and (IIe). UV $\lambda_{\text{max}}^{\text{EtOH}}$ m μ (saturated solution): (Ig) 279,311; (IIg) 277 and UV $\lambda_{\text{max}}^{\text{EtOH}}$ m μ (saturated solution): (Ie) 273, 312; (IIe) 278.

In contrast with the concurrent formation of a pair of the isomeric dipyridazo[4,5-*b*:4',5'-*e*]-1,4-dithiin derivatives in the reactions as described above, heating 3-methylthio-4-chloropyridazine-5-thiol (**15**) in ethanol for 3 hours formed 1,6-dimethylthiodipyridazo[4,5-*b*:4',5'-*e*]-1,4-dithiin (Ih)³ (mp 294°, colorless needles, 75% in yield), alone, whereas the isomer 1,9-dimethylthiodipyridazo[4,5-*b*:4',5'-*e*]-1,4-dithiin (IIh) (mp 275°, colorless needles, 80% in yield) was given by methylation of the compound (IIe). A similar result, the alone formation of 1,6-dimorpholinodipyridazo[4,5-*b*:4',5'-*e*]-1,4-dithiin (Ii) (mp 281°, yellow needles, 62% in yield), was also found in the case started with 3-morpholino-4-chloro-pyridazine-5-thiol (**16**), whereas the isomer 1,9-dimorpholinodipyridazo[4,5-*b*:4',5'-*e*]-1,4-dithiin (IIi) (mp 249°, pale yellow needles, 80% in yield) was derived from the compound (IIId).

Contrary to this, 3-methylthio-pyridazine-4,5-ditbiole (**17**) and 3-morpholinopyridazine-4,5-dithiole (**18**) furnished the concurrent formation of 1,6- and 1,9-disubstituted dipyridazo[4,5-*b*:4',5'-*e*]-1,4-dithiin, *i.e.* the former (**17**) was warmed in DMF at 80° for 5 hours to yield concurrently (Ih) (32% in yield) and (IIh) (22% in yield), and the latter (**18**) similarly gave a pair of Ii (31% in yield) and IIi (27% in yield).

Several kinds of the formation of the dipyridazo[4,5-*b*:4',5'-*e*]-1,4-dithiin derivatives described above might be divided in two classes according to the characters of the active intermediates involved in the reactions.

The first class of them, in which participate the starting materials, (**7**—**14**), proceed probably through the corresponding thioketo carbenes as active intermediate species. Furthermore, anyone of such thioketo carbenes, *e.g.* the dithioketo carbene, (IIIa₁ ↔ IIIa₂ ↔ IIIa₃) as shown in the Chart 1, might well be so reversibly convertible to the counterpart one (IIIb₁—IIIb₂) *via* a postulated activated intermediate state (IIIab or the like), that subsequently occurs the *per se* dimerization of the 1,3-dipolar species (IIIa₂) and (IIIb₂) and the reciprocal addition or crossed dimerization of them, both in 1,3-dipolar fashion and concurrently, to yield a pair of the isomeric dipyridazo[4,5-*b*:4',5'-*e*]-1,4-dithiins, while, in this case, any other

isomeric dipyridazo-1,4-dithiins such as dipyridazo[3,4-*b*:3',4'-*e*]-1,4-dithiin derivative, which could be produced by participation of another 1,3-dipolar species (IIIa₃) of dithioketo carbene in the dimerization was not detected. Lacked in any evidence in these cases, the interpretation might be acceptable by analogy on the basis of the facts that a few kinds of the keto-thioketo carbenes have trapped as the corresponding 1,3-dipolar cycloadducts such as 2-phenylimino-5-benzylpyridazo[4,5-*d*]-1,3-dithiol-4(5*H*)-one as previously reported.¹⁾

Chart 1

On the other hand, apparently similar reactions to the concurrent formation in which take part (17) and (18), together with those started with 15 and 16, constitute the second class of the cyclizations, as shown in the Chart 2.

The concurrently formed compounds, (Ih) and (IIh) presumably result through the relevant active intermediates, thioketo carbene species, in 1,3-dipolar fashions of dimerization as described above, however, existence of any reversible interconversion between the counterpart carbene species is scarcely inferred on the basis of the alone formation of Ih in the case started with 16.

The cyclization initiated with 18 is also similarly interpreted. In other words, during the course of the cyclization of 17 or 18, certainly exist independently the relevant carbene species as a pair, (IVa) and (IVb), generated from the unique source (17) or (18) in a definite mixing proportion, subsequently they combine by the two dimerization modes as described in the Chart 2.

Several reactions of the dipyridazo[4,5-*b*:4',5'-*e*]-1,4-dithiin derivatives showed that the ring system was fairly stable in acidic, neutral or weakly basic media reactions but so unstable in a strongly basic one as to bring cleavage of the ring. Chlorination of Ie or IIe with molecular chlorine in a hydrochloric acid-ethanolic medium, mercaptylation of Id or IId with thiourea in an ethanolic solution and the reaction of the same compound with morpholine

Chart 2

in ethanol, all of them so smoothly proceeded as to yield the expected products, respectively. In contrast with this, an attempted reaction of Id or IId with sodium benzylmercaptide, by heating them in benzene under reflux for several hours or even by stirring that in DMF at a room temperature for only an hour, with the intention of preparing the 1,6- (If) or 1,9-bisbenzylthio derivative (IIIf) was tried to be unsuccessful but to leave a complicated result, whereas, allowing them to react in an aq. alkaline ethanolic medium by stirring at a room temperature for 5 hours produced an unexpected compound, 3-chloro-4,5-bis(benzylthio)pyridazine (**19**)⁴ (36% and 41% in yield, respectively, based on Id and IId) with elimination of sulfur, instead of obtaining any intended product.

Any suggestion being scarcely offered for it, the reaction together with the interconversion between Ia and IIa presented on the preceeding paper,¹⁾ would develop our interest in further study on the chemistry of dipyridazo-1,4-dithiins.

Synthesis of 3,4-dichloro-5-benzylthiopyridazine (**10**), 4-chloro-5-mercapto- (**12**) and 4,5-dimercapto-3(2*H*)-pyridazinethiones (**13,14**), 4-chloropyridazine-5-thiol (**15,16**) and pyridazines-4,5-dithiol (**17,18**) and the related compounds were carried through an unambiguous route in the Chart 3 shown below.

The compound (**10**) was easily obtained by chlorination of 4-chloro-5-benzylthio-3(2*H*)-pyridazinone⁵⁾ with phosphorus oxychloride, while the compounds (**12,15,16**) were prepared by

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

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

debenzylation of 3,5-bis(benzylthio)-4-chloropyridazine (**32**), 3-methylthio-4-chloro-5-benzylthiopyridazine (**33**) and 3-morpholino-4-chloro-5-benzylthiopyridazine (**34**), with anhydrous aluminium chloride in dry-toluene, respectively.

3,4,5-tris(benzylthio)pyridazine (**26**)⁴ was hydrolyzed with ethanolic sodium hydroxide solution to give predominantly 3,5-bis(benzylthio)-4-pyridazinol (**29**), from which the compound (**32**) was derived by chlorination with phosphorus oxychloride.

The structural assignment of the isomeric relation ship between (29) and 3,4-bis(benzylthio)-5-pyridazinol was made by the fact that the mercaptylated compound of 32 was identified in all respects with 3,5-bis(benzylthio)-pyridazine-4-thiol (24), which was derived from 3-chloro-4-mercapto-5-benzylthiopyridazine (20) through the three steps *via* 3-chloro-4-(2-tetrahydropyranylthio)-5-benzylthiopyridazine (21) following* by 3,5-bis(benzylthio)-4-(2-tetrahydro-pyranylthio)-pyridazine (22). And the compound (20) was easily obtained by mono-mercaptylation of 10 with ethanolic sodium hydrosulfide solution at a room temperature.

3-methylthio-4-chloro-5-benzylthiopyridazine (**33**) and 3-morpholino-4-chloro-5-benzylthiopyridazine (**34**) were also prepared by analogous method in that of **32**, starting from 3-methylthio-4,5-bis(benzylthio)pyridazine (**27**) and 3-morpholino-4,5-bis(benzylthio)pyridazine (**28**), which were given by mercaptylation of **19** with thiourea following by methylation of it with methyl iodide, and by morpholination of **19** with morpholine, respectively.

On the other hand, the compounds (**13,17,18**) were obtained by debenzoylation of **26,27,28** in a usual procedure, respectively, while the compound (**14**) was derived by heating 2-methyl-4,5-dichloro-3(2*H*)-pyridazinone¹⁾ with phosphorus pentasulfide in dry-pyridine.

Experimental⁶⁾

1,6-Dichlorodipyridazo[4,5-*b*:4',5'-*e*]-1,4-dithiin (Id)—a) From Dipyridazo[4,5-*b*:4',5'-*e*]-1,4-dithiin-1,6(2*H*,7*H*)-dione (Ib): A suspension of Ib (2.5 g) in phosphorus oxychloride (30 ml) and *N,N*-dimethylaniline (5 ml) was heated under reflux for 2 hours.

On cooling, the reaction mixture was poured onto cracked ice. The precipitated solid was collected, washed with dil. sodium hydroxide solution, then with water and dried. The crude product was recrystallized from ethanol to give 2.3 g (78.9%) of Id⁷⁾ as pale green needles, mp 286° (decomp.). *Anal.* Calcd. for C₈H₂N₄S₂Cl₂: C, 33.23; H, 0.69; N, 19.38. Found: C, 33.25; H, 0.80; N, 19.35.

b) From Ie: A cooled mixture of concd. hydrochloric acid (5 ml) and methanol (7.5 ml) was saturated with gaseous hydrogen chloride at 0°. To the solution was added Ie (2.0 g), and then chlorine at 15–20° for 3 hours with magnetic stirring. The reaction mixture was diluted with water and neutralized with aq. ammonia at 0°. Deposited solid was collected, washed with water and recrystallized from ethanol to give 1.8 g (78.3%) of Id.

1,9-Dichlorodipyridazo[4,5-*b*:4',5'-*e*]-1,4-dithiin (IIId)—a) From Dipyridazo[4,5-*b*:4',5'-*e*]-1,4-dithiin-1,9(2*H*,8*H*)-dione (IIb): IIb (0.7 g) was allowed to react with phosphorus oxychloride (10 ml) and *N,N*-dimethylaniline (2 ml) in a similar manner as described above to obtain 0.6 g (75%) of IIId as pale yellow needles (dichloromethane), mp 239° (decomp.). *Anal.* Calcd. for C₈H₂N₄S₂Cl₂: C, 33.23; H, 0.69; N, 19.38. Found: C, 33.35; H, 0.85; N, 19.60.

b) From IIe: IIe (0.4 g) was allowed to react with chlorine in a solution of concd. hydrochloric acid (2 ml) and methanol (4 ml), saturated with gaseous hydrogen chloride at 0° in a similar manner as described above. After fractional recrystallization from dichloromethane, 0.3 g (75%) of IIId was obtained. A trace of mono-hydrate of IIId was also obtained as colorless needles, mp 235°. *Anal.* Calcd. for C₈H₄ON₄S₂Cl₂: C, 31.30; H, 1.31; N, 18.25. Found: C, 31.08; H, 1.06; N, 18.28.

Dipyridazo[4,5-*b*:4',5'-*e*]-1,4-dithiin-1,6(2*H*,7*H*)-dithione (Ie)—a) From (Id): Id (2.9 g) was heated under reflux with thiourea (1.7 g) in ethanol (50 ml) for 3 hours. On cooling, precipitated solid was collected, washed with ethanol and heated with 10% sodium hydroxide solution (20 ml) for 30 minutes. The resulting solution was diluted with water and filtered. The filtrate was acidified with concd. hydrochloric acid to pH=1. Precipitated solid was collected, washed with water. Purification was effected by dissolving in dil. sodium hydroxide solution to precipitate a solid, which was collected, washed with water, ethanol and dried to obtain 2.3 g (82.1%) of Ie as reddish solid, mp >300°. IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 3150–2900 (HN<, broad) 1222 (S=C<). *Anal.* Calcd. for C₈H₄N₄S₄: C, 33.78; H, 1.41; N, 19.70. Found: C, 33.85; H, 1.68; N, 19.68.

b) From If: To a solution of anhydrous aluminium chloride (4.0 g) in dry-toluene (75 ml) was added If (4.6 g) rapidly with stirring and the whole was kept at 60° for 6 hours. On cooling, to the reaction mixture was added water. Precipitated solid was collected, washed with water and ethanol to give 2.5 g (89.3%) of Ie. This compound was identical with Ie obtained from Id by IR spectrum.

Dipyridazo[4,5-*b*:4',5'-*e*]-1,4-dithiin-1,9(2*H*,8*H*)-dithione (IIe)—a) From IIId: IIId (0.15 g) was allowed to react with thiourea (0.14 g) in ethanol (5 ml) in a similar manner as described above to obtain 0.10 g (71.4%) of IIe as red solid, mp >300°. IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 3150–2900 (HN<, broad), 1121 (S=C<). *Anal.* Calcd. for C₈H₄N₄S₄: C, 33.78; H, 1.41; N, 19.70. Found: C, 33.89; H, 1.70; N, 19.62.

b) From IIIf: IIIf (0.6 g) was allowed to react with anhydrous aluminium chloride (0.9 g) in dry-toluene (10 ml) in a similar manner as described above to obtain 0.3 g (81.0%) of IIe. This compound was identical with IIe obtained from IIId by IR spectrum.

1,6-Bis(benzylthio)dipyridazo[4,5-*b*:4',5'-*e*]-1,4-dithiin (If)—To a solution of Ie (0.2 g) in 2.5% sodium hydroxide solution (6 ml) and ethanol (6 ml) was added benzylchloride (0.2 g) and the whole was stirred

6) All melting points are uncorrected. IR spectra were taken on Hitachi EPI-S₂ recording spectrometer in potassium bromide discs. UV spectra were taken on Shimadzu MPS-50 instrument in 95% EtOH. NMR spectra were measured on Japan Electron Optics Lab. C-60 spectrometer with tetramethylsilan (TMS) as an internal standard.

7) In the literature³⁾ mp 284–285° (decomp.), 24% in yield.

at a room temperature for an hour. Precipitated solid was collected, washed with water and recrystallized from ethanol to give 0.2 g (67.1%) of If as yellow needles, mp 178°. *Anal.* Calcd. for $C_{22}H_{16}N_4S_4$: C, 56.86; H, 3.46; N, 12.06. Found: C, 56.70; H, 3.51; N, 12.01.

1,9-Bis(benzylthio)dipyridazo[4,5-*b*:4',5'-*e*]-1,4-dithiin (IIf)—IIf (0.2 g) was allowed to react with benzylchloride (0.2 g) in a similar manner as described above to give 0.2 g (67.1%) of IIf as colorless needles (ethanol), mp 170°. *Anal.* Calcd. for $C_{22}H_{16}N_4S_4$: C, 56.86; H, 3.46; N, 12.06. Found: C, 56.80; H, 3.56; N, 11.88.

1,6-Bis(methylthio)dipyridazo[4,5-*b*:4',5'-*e*]-1,4-dithiin (Ih)—Ie (1.4 g) was allowed to react with methyl iodide (1.5 g) in a similar manner as described above to give 1.3 g (81.5%) of Ih as colorless needles (ethanol), mp 294°. ⁸⁾ *Anal.* Calcd. for $C_{10}H_8N_4S_4$: C, 38.45; H, 2.58; N, 17.94. Found: C, 38.61; H, 2.79; N, 17.98.

1,9-Bis(methylthio)dipyridazo[4,5-*b*:4',5'-*e*]-1,4-dithiin (IIh)—IIf (0.28 g) was allowed to react with methyl iodide (0.3 g) in a similar manner as described above to give 0.25 g (80.6%) of IIh as colorless needles, mp 275°. *Anal.* Calcd. for $C_{10}H_8N_4S_4$: C, 38.45; H, 2.58; N, 17.94. Found: C, 38.69; H, 2.76; N, 17.58.

1,6-Dimorpholinodipyridazo[4,5-*b*:4',5'-*e*]-1,4-dithiin (Ii)—A mixture of Id (0.29 g) and morpholine (0.5 g) in abs. ethanol (5 ml) was heated under reflux for 5 hours. On cooling, precipitated solid was collected, washed with water and recrystallized from ethanol to give 0.30 g (76.9%) of Ii as yellow needles, mp 281°. *Anal.* Calcd. for $C_{16}H_{18}O_2N_6S_2$: C, 49.21; H, 4.65; N, 21.52. Found: C, 49.24; H, 4.95; N, 21.60.

1,9-Dimorpholinodipyridazo[4,5-*b*:4',5'-*e*]-1,4-dithiin (IIi)—IIId (0.29 g) was allowed to react with morpholine (0.5 g) in abs. ethanol (5 ml) in a similar manner as described above to give 0.31 g (79.5%) of IIi as pale yellow needles, mp 249°. *Anal.* Calcd. for $C_{16}H_{18}O_2N_6S_2$: C, 49.21; H, 4.65; N, 21.52. Found: C, 49.25; H, 4.61; N, 21.48.

The Concurrent Formation of 2,7-Dibenzylidipyridazo[4,5-*b*:4',5'-*e*]-1,4-dithiin-1,6(2*H*,7*H*)-dione (Ia) and 2,8-Dibenzylidipyridazo[4,5-*b*:4',5'-*e*]-1,4-dithiin-1,9(2*H*,8*H*)-dione (IIa) from 2-Benzyl-4,5-dimercapto-3(2*H*)-pyridazinone (7)—7 (0.20 g) was heated under reflux in ethanol (10 ml) for 5 hours. The reaction mixture was concentrated to dryness *in vacuo*. To the residue was added dil. sodium hydroxide solution. Insoluble solid was extracted with dichloromethane. The dichloromethane solution was washed with water and dried over anhyd. sodium sulfate. The residue, obtained by concentration of the solvent, was chromatographed over silica gel to give 0.06 g (35.9%) of Ia as reddish orange needles, mp 265° and 0.03 g (17.9%) of IIa as reddish purple needles, mp 263°. These compounds were identical with an authentic sample in all respects, respectively.

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 4,5-Dimercapto-3(2*H*)-pyridazinone (8)—8 (1.6 g) was heated under reflux in ethanol (50 ml) for 5 hours. A pale reddish orange solid, separated from a yellow solution, was collected, washed with ethanol and dried, which yielded 0.5 g (40%) of Ib. The aq. ethanolic solution was concentrated to dryness *in vacuo* to give a yellow solid (mono-hydrate of IIb, which was easily dehydrated by heating in abs. ethanol for 3 hours to anhydrous 0.2 g (16%) of IIb. These compounds were identical with an authentic sample by comparison of IR and UV spectra, respectively.

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*]-1,4-dithiin-1,9(2*H*,8*H*)-dione (IIc) from 2-Methyl-4,5-dimercapto-3(2*H*)-pyridazinone (9)—9 (0.50 g) was warmed in DMF (5 ml) at 80° for 1 hour in a similar manner as described above to give 0.16 g (38.1%) of Ic and 0.10 g (23.8%) of IIc. These compounds were identical with an authentic sample in all respects, respectively.

The Concurrent Formation of Id and IIId—10 (2.7 g) was allowed to react with anhydrous aluminium chloride (2.9 g) in dry-toluene (50 ml) in a similar manner as mentioned before.

After chromatographic separation over silica gel in dichloromethane, 0.45 g (31.0%) of Id and 0.2 g (13.8%) of IIId was obtained. These compounds were identical with an authentic sample in all respects, respectively.

The Concurrent Formation of Ie and IIf—a) From 12: 12 (0.4 g) was heated under reflux in ethanol (100 ml) for 3 hours. Precipitated solid was collected, washed with water, and dried, which yielded 0.25 g (80.6%) of a mixture of Ie and IIf as reddish solid. This crude product was allowed to react with benzylchloride (0.26 g) in 2.5% sodium hydroxide solution (7 ml) and ethanol (7 ml). Precipitated solid was collected, washed with water and chromatographed over silica gel in dichloromethane to give 0.21 g (50.0%) of Ie and 0.10 g (23.8%) of IIf.

b) From 13: 13 (0.35 g) was heated under reflux in ethanol (10 ml) for 5 hours followed by benzylated with benzylchloride (0.27 g) in a similar manner as described above to obtain 0.20 g (43.5%) of Ie and 0.10 g (21.7%) of IIf.

These compounds were identical with an authentic sample in all respects, respectively.

8) in the literature³⁾ mp 286—287°.

The Concurrent Formation of 2,7-Dimethyldipyridazo[4,5-*b*:4',5'-*e*]-1,4-dithiin-1,6(2*H*,7*H*)-dione (Ig) and 2,8-Dimethyldipyridazo[4,5-*b*:4',5'-*e*]-1,4-dithiin-1,9(2*H*,8*H*)-dione (IIg)—14 (0.57 g) was warmed in DMF (5 ml) at 80° for 1 hour. The reaction mixture was diluted. Precipitated solid was collected, washed with dil. sodium hydroxide solution, then with water and dried, which was chromatographed over silica gel in dichloromethane to give 0.20 g (43.5%) of Ig as red small needles, mp >300° and 0.12 g (24.8%) of IIg as yellow needles, mp >300°. *Anal.* Calcd. for C₁₀H₈N₄S₄: C, 38.43; H, 2.58; N, 17.93. Ig, Found: C, 38.57; H, 2.72; N, 18.02. IIg, Found: C, 38.61; H, 2.45; N, 17.86.

The Formation of Ih from 15—15 (0.20 g) was heated under reflux in ethanol (50 ml) for 3 hours similar as described above. The crude product produced one-spot by TLC (silica gel in dichloromethane). Therefore, that was recrystallized from chloroform to give 0.12 g (75.0%) of Ih. This compound was identical with an authentic sample in all respects.

The Formation of Ii from 16—16 (0.23 g) was heated under reflux in ethanol (10 ml) for 3 hours similarly as described above to obtain 0.12 g (61.8%) of Ii. This compound was identical with an authentic sample, in all respects.

The Concurrent Formation of Ih and IIh from 17—17 (0.38 g) was warmed in DMF (5 ml) at 80° for 5 hours similarly as described above to give 0.10 g (32.2%) of Ih and 0.07 g (22.6%) of IIh. These compounds were identical with an authentic sample in all respects, respectively.

The Concurrent Formation of Ii and IIIi from 18—18 (0.23 g) was warmed in DMF (5 ml) at 80° for 3 hours similarly as above. After chromatographic separation over alumina in dichloromethane and THF (10:1), 0.06 g (30.7%) of Ii and 0.05 g (25.2%) of IIIi were obtained. These compounds were identical with an authentic sample in all respects, respectively.

The Reaction of Id with Sodium Benzylmercaptide Solution—To a sodium benzylmercaptide solution, containing benzylmercaptan (0.74 g) in 5% sodium hydroxide solution (24 ml) and ethanol (24 ml) was added Id (0.72 g) and the whole was stirred for 5 hours at a room temperature. Precipitated solid was collected, washed with water and dried, which was chromatographed over silica gel in benzene to give 0.1 g (62.5%) of sulfur as yellow crystals, mp 125–126°, and 0.71 g (35.5%) of 3-chloro-4,5-bis(benzylthio)-pyridazine (19) as colorless needles, mp 114°. This compound was identical with an authentic sample, in all respects.

The Reaction of IId with Sodium Benzylmercaptide Solution—IId (0.36 g) was allowed to react with sodium benzylmercaptide solution similarly as described above to give 0.04 g (50.0%) of sulfur and 0.41 g (41.0%) of 19.

3,4-Dichloro-5-benzylthiopyridazine (10)—A mixture of 4-chloro-5-benzylthio-3(2*H*)-pyridazinone (5.0 g) and phosphorus oxychloride (10 ml) was heated under gentle reflux for 20 minutes. The reaction mixture was treated similarly as described above to give 4.4 g (81.5%) of 10 as colorless pillars (cyclohexane), mp 156°. *Anal.* Calcd. for C₁₁H₈N₂SCl₂: C, 48.72; H, 2.97; N, 10.33. Found: C, 48.98; H, 3.09; N, 10.46.

4-Chloro-5-mercapto-3(2*H*)-pyridazinethione (12)—32 (2.5 g) was allowed to react with anhydrous aluminium chloride (2.7 g) in dry-toluene (40 ml) similarly as described above to obtain 0.8 g (66.6%) of 12 as yellow needles (benzene), mp >300°. IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 3115–2910 (HN<, broad), 2410 (SH). *Anal.* Calcd. for C₄H₃N₂S₂Cl: C, 27.18; H, 1.73; N, 15.70. Found: C, 27.18; H, 1.73; N, 15.47.

2-Methyl-4,5-dimercapto-3(2*H*)-pyridazinethione (14)—2-Methyl-4,5-dichloro-3(2*H*)-pyridazinone (5.4 g) was heated under gentle reflux with powdered phosphorus pentasulfide (40.0 g) in dry-pyridine (250 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 for 1 hour. On cooling, the solution was made alkaline by dil. sodium hydroxide solution, washed with ether and filtered. The filtrate was acidified with concd. hydrochloric acid to pH=1. Deposited solid was collected, washed with water and recrystallized from cyclohexane to give 2.5 g (43.8%) of 14 as yellow needles, mp 123–124°. IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 2400, 2175 (SH, doublet). *Anal.* Calcd. for C₅H₆N₂S₃: C, 31.60; H, 3.18; N, 14.75. Found: C, 31.77; H, 3.03; N, 14.63.

3-Methylthio-4-chloropyridazine-5-thiol (15)—33 (0.8 g) was allowed to react with anhydrous aluminium chloride (0.9 g) similarly as described above to give 0.5 g (82.1%) of 15 as yellowish green solid, mp 249° (decomp.). *Anal.* Calcd. for C₅H₅N₂S₂Cl: C, 31.19; H, 2.62; N, 14.55. Found: C, 31.10; H, 2.68; N, 14.72.

3-Morpholino-4-chloropyridazine-5-thiol (16)—34 (0.32 g) was allowed to react with anhydrous aluminium chloride (0.16 g) in dry-toluene (10 ml) in a similar manner as described above to give 0.12 g (52.1%) of 16 as dark yellow needles (benzene and cyclohexane), mp 267°. *Anal.* Calcd. for C₈H₁₀ON₃SCl: C, 41.40; H, 4.34; N, 18.13. Found: C, 41.12; H, 4.25; N, 18.26.

3-Methylthio-pyridazine-4,5-dithiol (17)—27 (2.2 g) was allowed to react with anhydrous aluminium chloride (1.9 g) to give 0.9 g (80.0%) of 17 as yellow needles, mp 222°. *Anal.* Calcd. for C₅H₆N₂S₃: C, 31.60; H, 3.18; N, 14.73. Found: C, 31.73; H, 3.31; N, 14.52.

3-Morpholino-pyridazine-4,5-dithiol (18)—28 (1.6 g) was allowed to react with anhydrous aluminium chloride (1.2 g) to give 0.8 g (86.9%) of 18 as yellowish green needles (ethanol), mp 196°. *Anal.* Calcd. for C₈H₁₁ON₃S₂: C, 41.93; H, 4.84; N, 18.33. Found: C, 42.12; H, 4.76; N, 18.23.

3-Chloro-5-benzylthiopyridazine-4-thiol (20)—To a solution of 40% aq. sodium hydrosulfide (5.3 g) in ethanol (150 ml) was added **10** (2.7 g) and the whole was stirred at a room temperature for 3 hours. The reaction mixture was concentrated to dryness *in vacuo*. To the residue was added water (200 ml). The aq. solution was acidified with concd. hydrochloric acid to precipitate a yellow solid, which was collected, washed with water and dissolved in dil. sodium hydroxide solution to remove an insoluble solid. The aq. alkaline clear solution was acidified with concd. hydrochloric acid to pH=1. Deposited solid was collected, washed with water and recrystallized from ethylacetate to give 2.2 g (81.5%) of **20** as yellow crystals, mp 168° (decomp.). *Anal.* Calcd. for $C_{11}H_9N_2S_2Cl$: C, 49.89; H, 3.37; N, 10.43. Found: C, 49.66; H, 3.72; N, 10.65.

3-Chloro-4-(2-tetrahydropyranyltio)-5-benzylthiopyridazine (21)—In a round-bottom flask, **20** (1.4 g) and dihydropyran (4.2 g) were placed. To the mixture was added a few drops of concd. hydrochloric acid and the whole was allowed to stand at a room temperature overnight. Precipitated solid was collected with an addition of abs. ether (50 ml) and recrystallized from benzene and cyclohexane to give 1.4 g (80.0%) of **21** as bitter orange plates, mp 135°. *Anal.* Calcd. for $C_{16}H_{17}ON_2S_2Cl$: C, 54.56; H, 4.85; N, 7.94. Found: C, 54.69; H, 5.11; N, 7.91.

3,5-Bis(benzylthio)-4-(2-tetrahydropyranyltio)pyridazine (22)—To a sodium benzylmercaptide suspension, previously prepared by heating benzylmercaptan (0.6 g) with powdered sodium amide (0.2 g) in dry-benzene (15 ml) was added **21** (1.1 g) and the whole was heated under reflux for 5 hours. On cooling, the reaction mixture was washed with water and dried over anhydrous sodium sulfate. The viscous residue, obtained by concentration of benzene *in vacuo* was recrystallized from ethylacetate to give 1.0 g (76.9%) of **22** as yellow needles, mp 139°. *Anal.* Calcd. for $C_{23}H_{24}ON_2S_3$: C, 62.69; H, 5.49; N, 6.36. Found: C, 62.73; H, 5.79; N, 6.40.

3-Morpholino-4-(2-tetrahydropyranyltio)-5-benzylthiopyridazine (23)—**21** (0.36 g) was heated under reflux with morpholine (0.40 g) in abs. ethanol (3 ml) for 3 hours. On cooling, precipitated solid was collected and recrystallized from benzene to give 0.25 g (62.5%) of **23** as yellow small needles, mp 184°. *Anal.* Calcd. for $C_{20}H_{25}O_2N_3S_2$: C, 59.53; H, 6.24; N, 10.41. Found: C, 59.73; H, 6.13; N, 10.87.

3,5-Bis(benzylthio)pyridazine-4-thiol (24)—a) From **22**: **22** (0.44 g) was heated under gentle reflux *ca.* 10% hydrochloric acid (10 ml) in ethanol (25 ml) for 1 hour. The reaction mixture was concentrated to almost dryness *in vacuo*. To the residue was added dil. sodium hydroxide solution and washed with benzene. The aq. alkaline solution was acidified with concd. hydrochloric acid to precipitate a yellow solid, which was collected, washed with water and recrystallized from ethanol to give 0.30 g (84.2%) of **24** as yellow crystals, mp 223°. *Anal.* Calcd. for $C_{18}H_{16}N_2S_3$: C, 60.64; H, 4.52; N, 7.85. Found: C, 60.78; H, 4.78; N, 8.04.

b) From **32**: **32** (0.20 g) was warmed with 70% sodium hydrosulfide (0.13 g) in DMF (5 ml) on a steam bath for 3 hours. On cooling, to the reaction mixture was added water and the solution was acidified with concd. hydrochloric acid to precipitate a yellow solid which was collected and dissolved in dil. sodium hydroxide solution to remove an insoluble solid. The aq. alkaline clear solution was acidified with concd. hydrochloric acid to pH=1. Deposited solid was collected, washed with water and recrystallized from ethanol to give 0.14 g (73.8%) of **24**.

3-Morpholino-5-benzylthiopyridazine-4-thiol (25)—a) From **23**: **23** (0.20 g) was allowed to react with *ca.* 10% hydrochloric acid (3 ml) in ethanol (10 ml) as mentioned above to give 0.11 g (68.9%) of **25** as yellow crystals (ethanol), mp 211°. *Anal.* Calcd. for $C_{15}H_{17}ON_3S_2$: C, 56.38; H, 5.37; N, 13.15. Found: C, 56.20; H, 5.59; N, 12.84.

b) From **34**: **34** (0.30 g) was allowed to react with 70% sodium hydrosulfide (0.2 g) in DMF (5 ml) to give 0.2 g (66.7%) of **25**.

3-Methylthio-4,5-bis(benzylthio)pyridazine (27)—**19** (17.9 g) was heated under reflux with thiourea (11.4 g) in abs. ethanol (300 ml) for 3 hours. On cooling, precipitated solid was collected, which was heated in 20% sodium hydroxide solution (50 ml) for 1 hour and filtered. The filtrate was diluted with water and methylated with methyl iodide (7.0 g) with an addition of methanol (100 ml) for 1 hour at a room temperature. Precipitated solid was collected washed with water and recrystallized from methanol to give 10.2 g (55%) of **27** as colorless small needles, mp 138°. *Anal.* Calcd. for $C_{19}H_{18}N_2S_3$: C, 61.74; H, 4.91; N, 7.58. Found: C, 61.90; H, 4.84; N, 7.31.

3-Morpholino-4,5-bis(benzylthio)pyridazine (28)—**19** (1.2 g) was heated at 80° with morpholine (3.0 g) for 5 hours. The reaction mixture was concentrated to dryness *in vacuo*. To the viscous residue was added benzene. The benzene solution was washed with water, dried over anhydrous sodium sulfate. The residue obtained by concentration of benzene, was recrystallized from benzene and petroleum ether to give 0.9 g (65.7%) of **28** as pale yellow crystals, mp 103–105°. *Anal.* Calcd. for $C_{22}H_{23}ON_3S_2$: C, 64.51; H, 5.66; N, 10.26. Found: C, 64.64; H, 5.72; N, 10.02.

3,5-Bis(benzylthio)-4-pyridazinol (29)—**26** (13.2 g) was heated under reflux with 20% sodium hydroxide solution (60 ml) in ethanol (800 ml) for 5 hours. The reaction mixture was concentrated to almost dryness *in vacuo*. The viscous residue was diluted with water, and washed with benzene. The aq. alkaline solution was acidified with concd. hydrochloric acid to precipitate a solid, which was collected, washed with water and fractionally recrystallized from ethanol to give 4.5 g (44.1%) of **29** as yellow crystals, mp 199°.

Anal. Calcd. for $C_{18}H_{16}ON_2S_2$: C, 63.47; H, 4.74; N, 8.24. Found: C, 63.31; H, 4.42; N, 8.10. And from the mother liquor, 1.5 g (16.7%) of 3,4-bis(benzylthio)-5-pyridazinol as colorless needles, mp 184°. *Anal.* Calcd. for $C_{18}H_{16}ON_2S_2$: C, 63.47; H, 4.74; N, 8.24. Found: C, 63.67; H, 4.89; N, 8.11.

3-Methylthio-5-benzylthio-4-pyridazinol (30)—**27** (7.4 g) was allowed to react with 20% sodium hydroxide solution (40 ml) in ethanol (500 ml) similarly as described above to obtain 2.3 g (44.2%) of **30** as yellow needles, mp 179°. *Anal.* Calcd. for $C_{12}H_{12}ON_2S_2$: C, 54.71; H, 4.59; N, 10.64. Found: C, 54.87; H, 4.81; N, 10.42. And 0.7 g (13.4%) of 3-methylthio-4-benzylthio-5-hydroxypyridazine as almost colorless needles, mp 194°. *Anal.* Calcd. for $C_{12}H_{12}ON_2S_2$: C, 54.71; H, 4.59; N, 10.64. Found: C, 54.41; H, 4.78; N, 10.39.

3-Morpholino-5-benzylthio-4-pyridazinol (31)—**28** (6.0 g) was allowed to react with 20% sodium hydroxide solution (30 ml) in ethanol (200 ml) similarly as described above to obtain 1.5 g (33.3%) of **31** as colorless needles, mp 194°. *Anal.* Calcd. for $C_{15}H_{17}O_2N_3S$: C, 59.37; H, 5.65; N, 13.85. Found: C, 59.13; H, 5.56; N, 13.65. And 0.5 g (11.1%) of 3-morpholino-4-benzylthio-5-pyridazinol as yellowish orange needles, mp 175°. *Anal.* Calcd. for $C_{15}H_{17}O_2N_3S$: C, 59.37; H, 5.65; N, 13.85. Found: C, 59.05; H, 5.52; N, 12.11.

3,5-Bis(benzylthio)-4-chloropyridazine (32)—**29** (2.7 g) was allowed to react with phosphorus oxychloride (10 ml) in a similar manner as described above to give 2.5 g (87.1%) of **32** as yellow needles (cyclohexane), mp 156—158°. *Anal.* Calcd. for $C_{18}H_{15}N_2S_2Cl$: C, 60.22; H, 4.21; N, 7.80. Found: C, 60.50; H, 4.21; N, 7.61.

3-Methylthio-4-chloro-5-benzylthiopyridazine (33)—**30** (1.0 g) was allowed to react with phosphorus oxychloride (5 ml) similarly as described above to give 0.6 g (58.0%) of **33** as pale yellow crystals (cyclohexane), mp 114°. *Anal.* Calcd. for $C_{12}H_{11}N_2S_2Cl$: C, 51.12; H, 3.93; N, 9.94. Found: C, 51.41; H, 4.06; N, 9.72.

3-Morpholino-4-chloro-5-benzylthiopyridazine (34)—**31** (0.5 g) was allowed to react with phosphorus oxychloride (3 ml) to give 0.4 g (74.0%) of **34** as colorless crystals (cyclohexane), mp 127°. *Anal.* Calcd. for $C_{15}H_{16}ON_3S_2Cl$: C, 56.00; H, 5.01; N, 13.06. Found: C, 55.81; H, 5.03; N, 12.92.

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