[Chem. Pharm. Bull. 18(12)2420—2430(1970)]

UDC 547.852.2.04 : 547.842.07

Synthesis of Pyridazine Derivatives with Sulfur–Containing Substituent. IV.[1] The Concurrent Formation of Dipyridazo[3,4-*b*:3′,4′-*e*]-1,4-dithiin and Dipyridazo[3,4-*b*:4′,3′-*e*]-1,4-dithiin Derivatives by Starting with 3-Chloro-4-mercapto-5-substituted Pyridazines. (3)

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(Received May 9, 1970)

3-Chloro-4-mercapto-5-ethoxypyridazine (**1**) was heated under reflux in abs. ethanol for three hours to form concurrently four products with novel rings in the dipyridazo-1,4-dithiin system, 4,9-diethoxydipyridazo[3,4-*b*:3′,4′-*e*]-1,4-dithiin (pale yellow needles, mp 211°, 13% in yield) (Ia), 4,6-diethoxydipyridazo[3,4-*b*:4′,3′-*e*]-1,4-dithiin (colorless needles, mp 260°, 12% in yield) (IIa), dipyridazo[3,4-*b*:3′,4′-*e*]-1,4-dithiin-4,9(1*H*,6*H*)-dione (colorless solid, mp>300°, 24% in yield) (Ib), and dipyridazo[3,4-*b*:4′,3′-*e*]-1,4-dithiin-4,6(1*H*,9*H*)-dione (colorless solid, mp>300°, 16% in yield) (IIb). Structural assignment of the compounds, Ia, IIa, Ib and IIb, was confirmed by their physico-chemical constants and chemical experimental evidences.

Similar concurrent formations of an isomeric pair of 4,9-disubstituted dipyridazo-[3,4-*b*:3′,4′-*e*]-1,4-dithiins (I series isomers) and 4,6-disubstituted dipyridazo[3,4-*b*:4′,3′-*e*]-1,4-dithiins (II series ones) were also observed in those cases in which heating 3,5-dichloro-4-mercaptopyridazine (**3**), 3-chloro-4-mercapto-5-benzylthiopyridazine (**4**) and 3-chloro-4-mercapto-5-morpholinopyridazine (**5**) in similar reaction conditions (heating in proper polar solvents for proportionatd periods) formed a pair of the 4,9-dichloro- (colorless needles, mp 275°, only trace in yield) (Ic) and 4,6-dichloro derivative (pale yellow needles, mp 307° (decomp.), only trace in yield) (IIc), 4,9-dibenzylthio- (yellow crystals, mp 230°, 29% in yield) (Id) and 4,6-dibenzyl derivative (red crystals, mp 252°, 23% in yield) (IId), and 4,9-dimorpholino- (colorless crystals, mp 268°, 38% in yield) (Ie) and 4,6-dimorpholino derivative (colorless needles, mp 291°, 25% in yield) (IIe), respectively.

A rather complex cyclization furnishing the concurrent formation of two pairs of the dipyridazo-1,4-dithiin derivatives was found in the reaction of heating 3-chloro-4,5-dimercaptopyridazine (**6**) in a similar reaction condition, followed by benzylation, in which a pair of the derivatives with another novel ring, dipyridazo[3,4-*b*:4′,5′-*e*]-1,4-dithiin, the 4,9-dibenzylthio- (colorless plates, mp 168°, 5% in yield) (VI) and 4,6-dibenzylthio derivative (yellow needles, mp 210°, 11% in yield) (VII) and another pair of derivatives with a known ring, dipyridazo[4,5-*b*:4′,5′-*e*]-1,4-dithiin, the 1,6-dibenzylthio- (yellow needles, mp 178°, 19% in yield) (IV) and the 1,9-dibenzylthio derivative (colorless needles, mp 170°, 9% in yield) (V) and none of Id and IId or 1,6-dichlorodipyridazo-[4,5-*b*:4′,5′-*e*]-1,4-dithiin (If) and 1,9-dichloro derivative (IIf) was detected.

NMR spectra of some dibenzylthiodipyridazo-1,4-dithiin derivatives were compared.

A discussion of the cyclization mechanism involved in these reactions is also proposed.

It has been previously reported that the concurrent formations of dipyridazo[4,5-*b*:4′,5′-*e*]-1,4-dithiin-1,6(2*H*,7*H*)-dione and the isomeric 1,9(2*H*,8*H*)-dione derivatives and other 1,6-disubstituted dipyridazo[4,5-*b*:4′,5′-*e*]-1,4-dithiin and the isomeric 1,9-disubstituted-derivatives were furnished by heating appropriate starting materials, such as 4-chloro-5-mercapto-, 4-mercapto-5-chloro-, or 4,5-dimercaptopyridazines, in proper polar solvents for proportionate periods, and some of the cyclizations might proceed through the 1,3-dipolar addition of a pair of the thioketo carbenes in an equilibrium consisted of a generated active intermediate and a reversibly converted one, while the others went on similarly except a characteristic feature of the pair of the carbenes generated both but competitively from an

1) Part III: K. Kaji and M. Kuzuya, *Chem. Pharm. Bull.* (Tokyo), **18**, 970 (1970).
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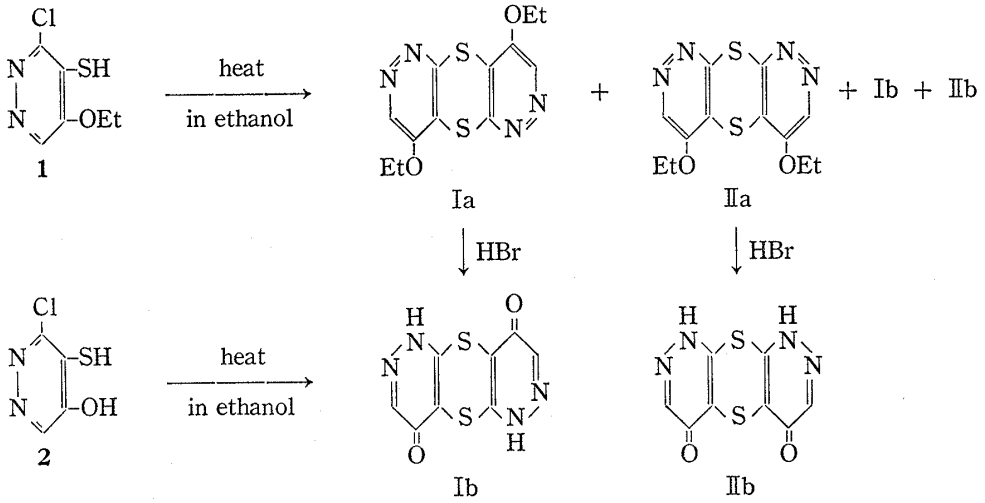
unique substrate by two elimination modes of hydrogen sulfide and scarcely converted into each other.

This paper deals with another cyclization reactions furnishing the concurrent formations of an isomeric pair of the compounds with novel rings belonging to the dipyridazo-1,4-dithiin system,[3] dipyridazo[3,4-*b*:3′,4′-*e*]-1,4-dithiin and dipyridazo[3,4-*b*:4′,3′-*e*]-1,4-dithiin, and a rather complex cyclization forming concurrently two pairs of the compounds, one of which holding another novel ring in the system, dipyridazo[3,4-*b*:4′,5′-*e*]-1,4-dithiin, and the other a known ring, dipyridazo[4,5-*b*:4′,5′-*e*]-1,4-dithiin, with a proposal of active intermediates possibly involved in the cyclizations.

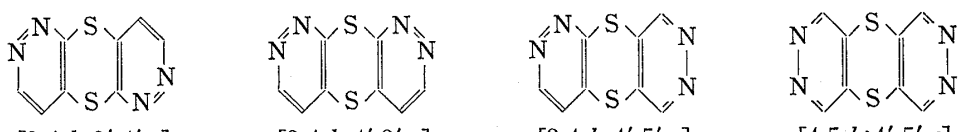
3-Chloro-4-mercapto-5-ethoxypyridazine (**1**) was heated under reflux in abs. ethanol for three hours, and separation and purification of the reaction mixture were effected to give two neutral compounds with the same elemental analysis value for $C_{12}H_{12}O_2N_4S_2$, *i.e.*, pale yellow needles (A) (mp 211° and 13% in yield) and colorless needles (B) (mp 260° and 12% in yield), and also two acidic compounds with the same elemental analysis value for $C_8H_4O_2N_4S_2$, both colorless solids mp>300° *i.e.*, (C) (IR ν_{max}^{KBr} cm^{-1}: 1580 (>C=O, broad) and 24% in yield) and (D) (IR ν_{max}^{KBr} cm^{-1}: 1595 (>C=O, broad) and 16% in yield).

Structural assignment of the isomeric compounds, A and B to 4,9-diethoxydipyridazo-[3,4-*b*:4′,3′-*e*]-1,4-dithiin (Ia) and 4,6-diethoxydipyridazo[3,4-*b*:4′,3′-*e*]-1,4-dithiin (IIa) respectively, was established by the following physico-chemical constants and chemical experimental facts.



These two compounds showed similar characteristic features in infrared(IR), ultraviolet (UV), nuclear magnetic resonance (NMR) and mass spectra. A: UV λ_{max}^{EtOH} mμ (log ε): 246 (4.26), 273 (4.49), NMR (in $CDCl_3$) τ: 8.43 (6H, triplet, J=7.5 cps, $-OCH_2-\underline{CH_3}$), 5.57 (4H, quartet J=7.5 cps, $-O\underline{CH_2}CH_3$), 1.24 (2H, singlet, ring-H) and Mass Spectrum, *m/e*: 308 (M^+). B: UV λ_{max}^{EtOH} mμ (log ε): 256 (4.24), 279 (4.43), NMR (in $CDCl_3$) τ: 8.44 (6H, triplet, J=7.5 cps,$-OCH_2\underline{CH_3}$), 5.59 (4H, quartet, J=7.5 cps, $-O\underline{CH_2}CH_3$), 1.22 (2H, singlet, ring-H) and Mass Spectrum *m/e*: 308 (M^+).

3) All possible isomeric dipyridazo-1,4-dithiin rings can be depicted with the corresponding prefixes as follows:



[3,4-*b*:3′,4′-*e*] [3,4-*b*:4′,3′-*e*] [3,4-*b*:4′,5′-*e*] [4,5-*b*:4′,5′-*e*]

A and B both easily hydrolyzed by heating with concentrated hydrobromic acid to give the deethylated products, Ib (colorless solid, mp>300°, IR ν_{max}^{KBr} cm^{-1}: 3150—2900 (–NH, broad), 1580 (>C=O, broad), 70% in yield) and IIb (colorless solid, mp>300°, IR ν_{max}^{KBr} cm^{-1}: 3170—2920 (–NH, broad), 1595 (>C=O, broad), 55% in yield) respectively, and the two acidic products described above, C and D proved to be identical with Ib and IIb by comparison of their IR spectra correspondingly.

Here it might be reasonably assumed that the structures of Ib and IIb are assigned to dipyridazo[3,4-*b*:3′,4′-*e*]-1,4-dithiin-4,9(1H,6H)-dione (Ib) and dipyridazo[3,4-*b*:4′3′-*e*]-1,4-dithiin-4,6(1H,9H)-dione (IIb) respectively, because a characteristic frequency of the carbonyl group in the IR spectrum of Ib shows a fall of 15 cm^{-1} compared with that of IIb, and the similar lowing effects in the frequency of carbonyl group, ascribable to the influence of olefinic or aryl conjugation to the group,[4] are also observed in the IR spectra of dipyridazo[4,5-*b*:4′,5′-*e*]-1,4-dithiin-1,6(2H,7H)-dione and dipyridazo[4,5-*b*:4′,5′-*e*]-1,4-dithiin-1,9(2H,8H)-dione (a decrement between the two frequencies of the carbonyl group: 10 cm^{-1}), the 2,7-dibenzyl derivative of the former and the 2,8-dibenzyl derivative (the decrement: 10 cm^{-1}) and the 2,7-dimethyl derivative and the 2,8-dimethyl derivative (the decrement: 20 cm^{-1}).[5] Furthermore, Ib indeed proved to be identical with the unique product obtained in fairly food yield by heating 3-chloro-4-mercapto-5-hydroxypyridazine (**2**) under reflux in abs. ethanol for five hours, without any contamination of the isomers, such as IIb by comparison of their IR spectra. Then IIb should be assigned to dipyridazo[3,4-*b*:4′,3′-*e*]-1,4-dithiin-4,6(1H,9H)-dione (IIb) accordingly A and B to 4,9-diethoxydipyridazo[3,4-*b*:3′,4′-*e*]-1,4-dithiin (Ia) and 4,6-diethoxydipyridazo[3,4-*b*:4′,3′-*e*]-1,4-dithiin (IIa) respectively.

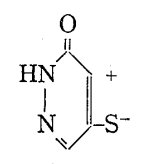
The concurrent formation of Ia and IIa, together with that of the corresponding deethylated compounds, Ib and IIb, was thus established by starting with **1** in the reaction condition concerned.

An attempted cyclization starting with 3,5-dichloro-4-mercaptopyridazine (**3**) in a similar reaction condition or heating in abs. ethanol was carried but to give a poor result in which the formation of 4,9-dichlorodipyridazo[3,4-*b*:3′,4′-*e*]-1,4-diithin (Ic) (colorless needles, mp 275°) and 4,6-dichlorodipyridazo[3,4-*b*:4′,3′-*e*]-1,4-dithiin (IIc) (pale yellow needles, mp 307° (decomp.) was only noticed by TLC pre-examination, together with the formation of a small amount of 1,6-dichloro- (If), 1,9-dichlorodipyridazo[4,5-*b*:4,5-*e*]-1,4-dithiin (IIf) and a fairly large amount of tarry products, and indeed Ic and IIc were not stable in ethanolic solution at a room temperature, although they were obtained by chlorination of Ib and IIb with phosphorus oxychloride in rather good yield, 65% and 73% respectively.

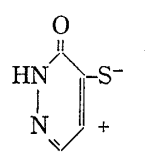
Another concurrent formation of a pair of these dipyridazo-1,4-dithiin derivatives was also observed in those cases where 3-chloro-4-mercapto-5-benzylthiopyridazine (**4**)[1] was heated at *ca.* 100° in abs. isopropanol for ten hours to form 4,9-dibenzylthiodipyridazo[3,4-*b*:3′,4′-*e*]-

4) L.J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley & Sons, Inc., 1954, pp. 114—138.

5) This discussion means that during the course of the reaction a contribution of a crossed dimerization between two dithioketo carbenes, ($IIIa_1$) and ($IIIb_3$), from which VII_0 is cyclized, is probably greater than that of another dimerization between (IIa_1) and ($IIIc_1$), from which VI_0 is formed, in other words, the yield of VII_0 would be higher than that of VI_0, on the premise that the alternative two pathes to which $IIIb_1$ participate would never be chosen for the formation of VI_0 and $VIII_0$ as described below, and this assumption is mainly based on the experimental fact that a contribution of a ketothioketo carbene (the 1,3-dipolar form) ($IIIf_0$), a similar type to $IIIb_3$, to the two cyclization yielding dipyridazo[4,5-*b*:4,5-*e*]-1,4-dithiin-1,6-dione and dipyridazo[4,5-*b*:4′,5′-*e*]-1,9-dione, was greater than that of another carbene ($IIIg_0$), a similar one to $IIIc_1$, to the reactions starting with 4-chloro-5-mercapto- and 4-mercapto-5-chloro-3(2*H*)-pyridazinone.[6]

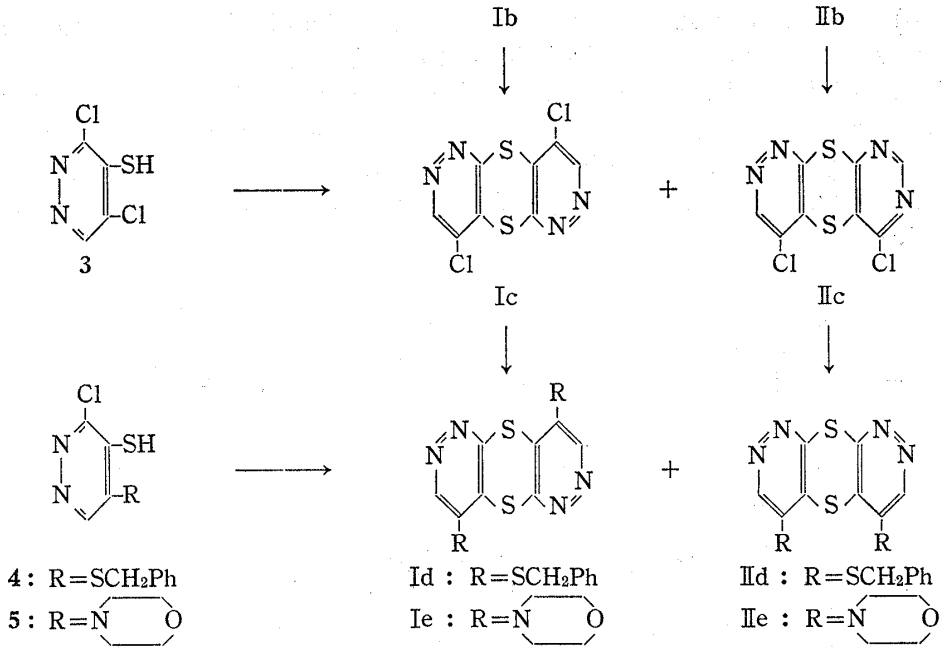


$IIIf_0$



$IIIg_0$

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



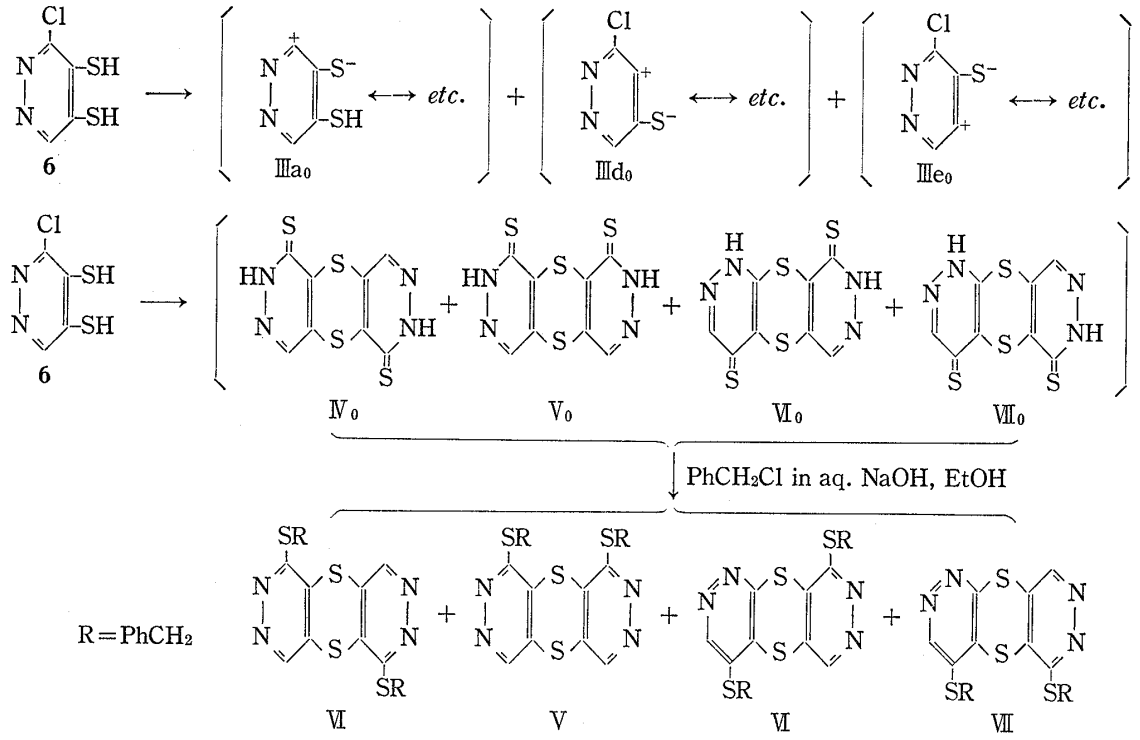
1,4-dithiin (Id) (yellow crystals, mp 230°, 29% in yield) and 4,6-dibenzylthiodipyridazo[3,4-*b*:4′,3′-*e*]-1,4-dithiin (IId) (red crystals, mp 252°, 23% in yield) or 3-chloro-4-mercapto-5-morpholinopyridazine (**5**) was refluxed in abs. ethanol three hours to yield 4,9-dimorpholinodipyridazo[3,4-*b*:3′,4′-*e*]-1,4-dithiin (Ie) (colorless crystals, mp 268°, 38% in yield) and 4,6-dimorpholinodipyridazo[3,4-*b*:4′,3′-dithiin (IIe) (colorless needles, mp 291°, 25% in yield). Assignment of these two sets of the products, Id and IId, or Ie and IIe, to the corersponding structures depicted was confirmed by mixed melting point tests and by comparison of their IR spectra and *Rf* values of TLC with those of the corresponding authentic specimens prepared by benzylthiolation or morpholination of Ic and IIc, respectively. These cyclization consequences show a distinct contrast to that in which the unique cyclized compound, such as 1,6-dimethylthio- or 1,6-dimorpholinodipyridazo[4,5-*b*:4′,5′-*e*]-1,4-dithiin was formed when 3-methylthio- or 3-morpholino-4-chloro-5-mercaptopyridazine was submitted to a similar reaction condition.[1] A performed benzylthiolation of Ic or IIc, though the yield of Id or IId was rather poor, was also a noticeable contrast to a completely failed benzylthiolation of (If) of (IIf).[1]

Heating 3-chloro-4,5-dimercaptopyridazine (**6**) in abs. ethanol under reflux for five hours afforded a relatively complex result and it can be rather otherwise considering that the starting material might be possibly underwent the two modes of decomposition, an elimination of hydrogen chloride and that of hydrogen sulfide, to generate not a few set of active intermediates ($II_{ao}\leftrightarrow$*etc.*, $II_{do}\leftrightarrow$*etc.*, $III_{eo}\leftrightarrow$*etc.*) for the cyclizations.

The reaction mixture obtained was so difficult to separate into the individual components that it was sofort benzylated in a usual procedure and the benzylated compounds mixture was submitted on chromatography over silica gel in dichloromethane to separate into four products; they were, common in an elemental analysis value for $C_{22}H_{16}N_4S_4$, yelolw needles (mp 178°, 19% in yield) (A′), colorless needles (mp 170°, 9% in yield) (B′), colorless plates (mp 168°, 5% in yield) (C′) and yellow needles (mp 210°, 11% in yield) (D′). A′ and B′ proved to be identical with 1,6-dibenzylthiodipyridazo[4,5-*b*:4′,5′-*e*]-1,4-dithiin (IV)[1] and 1,9-dibenzylthiodipyridazo[4,5-*b*:4′,5′-*e*]-1,4-dithiin (V)[1] respectively, based on the mixed melting point tests and comparison of their IR spectra and *Rf* of values of TLC.

Next each of the NMR spectra of C′ and D′ shows the presence of asymmetric ring junctions and two S-benzylthio substituents in the hetero ring, *i.e.* (in $CDCl_3$) τ: C′; 5.67 (2H, singlet, S–CH_2–), 5.33 (2H, singlet, S–CH_2–) and D′; 5.67 (2H, singlet, S–CH_2–), 5.34 (2H,

singlet, S–CH_2–) and this suggests that the assignment of C′ and D′ should be, not to Id or IId, but to 4,9-dibenzylthiodipyridazo[3,4-*b*:4′,5′-*e*]-1,4-dithiin (VI) or 4,6-dibenzylthiodipyridazo-[3,4-*b*:4′,5′-*e*]-1,4-dithiin (VII), the compound with another novel ring in the dipyridazo-1,4-dithiin ring, though difficult to assign alternatively, and further they are actually different from Id or IId in any respect. In addition, it is tentatively mentioned that C′ and D′ might be assignable to VI and VII, respectively, only not exceeded an assumption based on the experimental fact.[5]



The concurrent formation of two pairs of the isomeric dipyridazo-1,4-dithiin, *i.e.*, dipyridazo[4,5-*b*:4′,5′-*e*]-1,4-dithiin-1,6-(2H,7H)-dithione (IV_0) and dipyridazo[4,5-*b*:4′,5′-*e*]-1,4-dithiin-1,9(2*H*,8*H*)-dithione (V_0) and dipyridazo[3,4-*b*:4′,5′-*e*]-1,4-dithiin-4,9(1*H*,8*H*)-dithione (VI_0) and dipyridazo[3,4-*b*:4′,5′-*e*]-1,4-dithiin-4,6(1*H*,7*H*)-dithione(VII_0), was thus furnished by starting with **6** in a similar reaction condition used as in other cases though but an indirect demonstration.

Other noticeable result observed in the reaction was an unsuccessful isolation of another pairs of the dipyridazo-1,4-dithiins, such as Id and IId, and If and IIf, notwithstanding apparently being expectable of their formation when taken into consideration of the cyclization

Table I. NMR Spectra of Some Dibenzylthiodipyridazo-1,4-dithiin (in $CDCl_3$, τ)

	IV	V	Id	IId	VI	VII
S–CH_2–	5.33(4H,s)	5.36(4H,s)	5.50(4H,s)	5.51(4H,s)	5.33(2H,s) 5.67(2H,s)	5.34(2H,s) 5.67(2H,s)
Ring-H	1.15(2H,s)	1.21(2H,s)	1.16(2H,s)	1.20(2H,s)	1.18(1H,s) 1.20(1H,s)	1.20(1H,s) 1.28(1H,s)

R=$C_6H_5CH_2$–

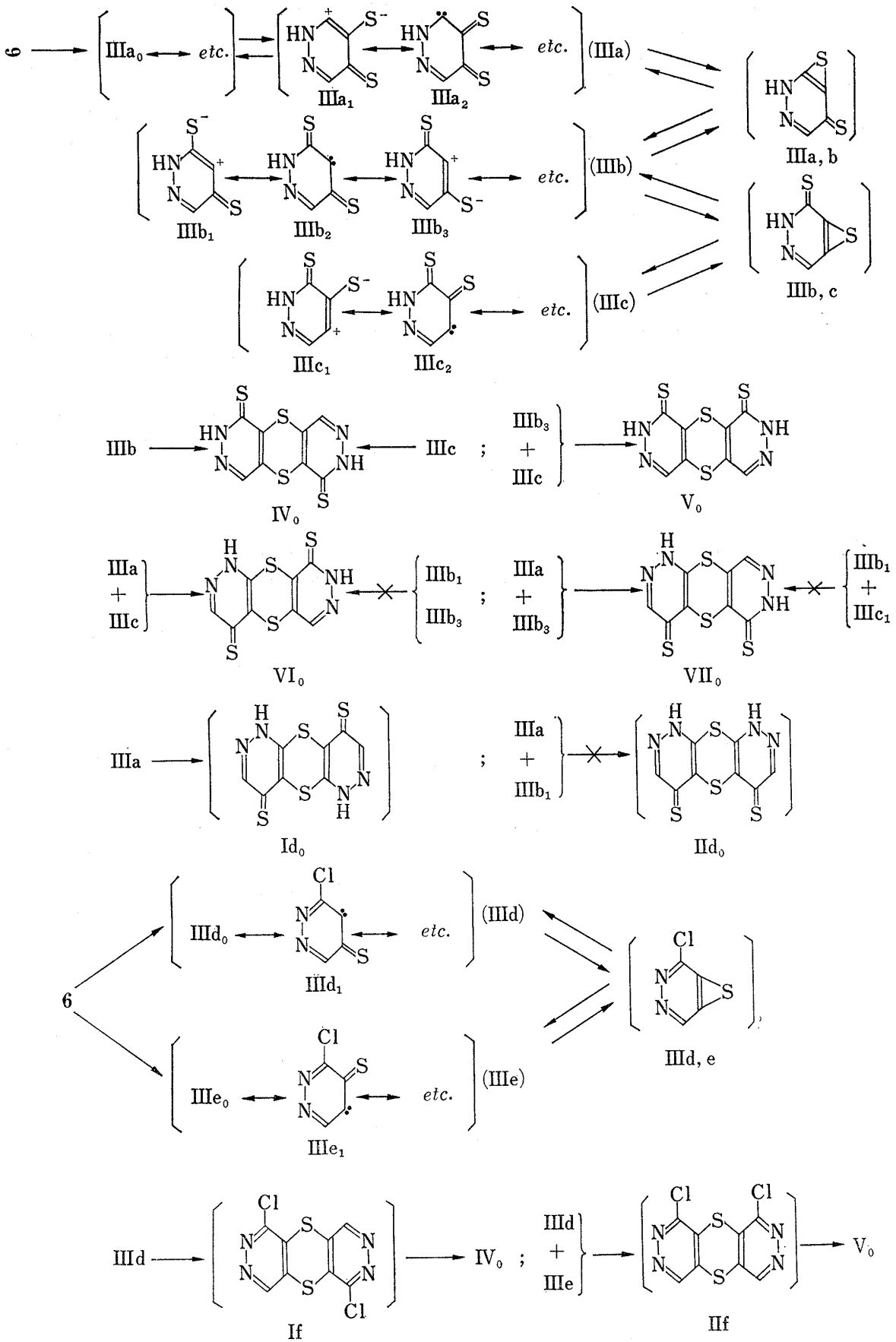


Chart 1

starting with 3,4-dichloro-5-mercaptopyridazine, 4,5-dimercapto-3(2*H*)-pyridazinethione, or 2-methyl-4,5-dimercapto-3(2*H*)-pyridazinethione.[1)]

The NMR spectra of some related dibenzylthiopyridazo-1,4-dithiins are summarized in the Table I.

There are apparently two possible mechanism involving some thioketo carbenes for the complex cyclization starting with **6**. One path involves three kinds of the dithioketo carbenes among which one species (IIIa) generated is reversibly converted to the second (IIIb) and to the third one (IIIc), probably *via* corresponding activated intermediate states, IIIa,b and IIIb,c or the like, successively, followed by their dimerization,per se or reciprocally, to form concurrently two pairs of dipyridazo-1,4-dithiins, IVo, Vo, VIo and VIIo, as shown in the Chart 1.

Another possibility is a competitive participation of the two chlorothioketo carbenes, IIId and IIIe, generated independently but reversibly converted, *via* a similar activated intermediate state, IIId, e, to each other, with subsequent dimerization and nucleophilic substitution by nascent hydrogen sulfide to form If and IIf, and consecutively IVo and Vo.

Another pathway through which VIo or VIIo, is formed by the crossed dimerization between $IIIb_1$ and $IIIb_3$, or $IIIb_1$ and $IIIc_1$, respectively, is thought probably not to be passed, as a contribution of $IIIb_1$ to the resonance in IIIb would be neglegibly small, when viewed from the experimental fact[1)] that in the reaction starting with 4-chloro-5-mercapto-3(2*H*)-pyridazinethione, followed by benzylation, during which IIIb would be also generated formally, neither VI nor VII was detected. Similarly a cyclization leading to the formation of IId seems not to occur, however, that of Id *via* IIIa would be rather expected.

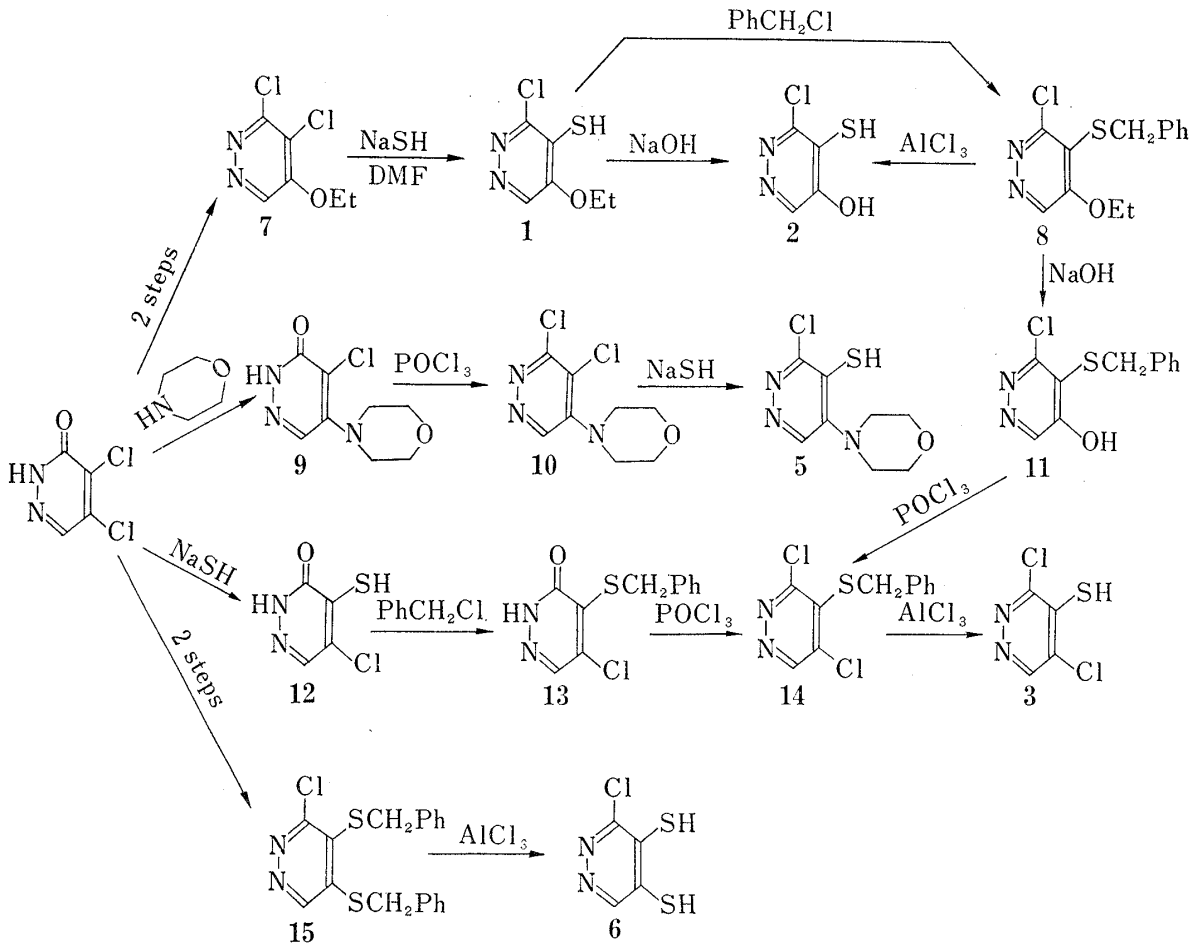


Chart 2

This interpretation for the reaction accounts considerably for the isolation of the four products, IV, V, VI and VII, and might be appreciated on the analogy of the reactions to which participate some trapped thioketo carbenes,[6,7] though lacked in evidence and remained unsettled in no detection of Id, If or IIf in the case.

Synthesis of the starting materials, some 3-chloro-4-mercapto-5-substituted pyridazines (**1**—**6**) an the related compounds was carried through an unambiguous route shown in the Chart 2.

1 (mp 139° (decomp.), 74% in yield) was easily prepared by mercaptylation with sodium hydrosulfide in DMF of 3,4-dichloro-5-ethoxypyridazine,[8] and hydrolyzed with ethanolic aq. sodium hydroxide solution to give **2** (mp 132° (decomp.), 65% in yield). **2** was also obtained without difficulty by dealkylation of 3-chloro-4-benzylthio-5-ethoxypyridazine (**8**), the benzylated derivative of **1**, by warming with anhydrous aluminium chloride with stirring in dry-toluene, during which occured a succeessive elimination of the both alkyl groups attached to the different atoms in the molecule, **8**. **3** (mp 119° (decomp.), 66% in yield) was prepared by debenzylating 3,5-dichloro-4-benzylthiopyridazine (**14**) similarly, although each preparative procedure of the latter needed a couple of steps of reactions, when started with either **8** or 4-mercapto-5-chloro-3(2*H*)-pyridazinone (**12**),[6] only each step, hydrolysis and chlorination, or benzylation and chlorination, respectively involved in the corresponding procedure, was carried smoothly.

The preparation of **5** (mp 155° (decomp.), 71% in yield) was effected easily by mercaptylation of 3,4-dichloro-5-morpholinopyridazinone (**10**), which was derived also without any difficulty from 4-chloro-5-morpholino-3(2*H*)-pyridazinone (**9**) by a usual chlorination with phosphorus oxychloride.

6 (mp 148° (decomp.), 66% in yield) was obtained without difficulty by a similar debenzylation of 3-chloro-4,5-bis(benzylthio) pyridazine (**15**).[6]

Further work is in progress on the cyclization producing the dipyridazo-1,4-dithiin derivatives by starting with another kind of appropriate compounds and will be reported at a later date.

Experimental[9]

The Concurrent Formation of 4,9-Diethoxydipyridazo[3,4-*b*:3′,4′-e]-1,4-dithiin (Ia) and 4,6-Diethoxydipyridazo[3,4-*b*:4′,3′-e]-1,4-dithiin (IIa) from 3-Chloro-4-mercapto-5-ethoxypyridazine (1)——1 (1.90 g) was heated under reflux in abs. ethanol (50 ml) for 3 hours.

The reaction mixture was concentrated to dryness *in vacuo*. To the residue was added 1% sodium hydroxide solution to separate an insolble solid and aq. alkaline solution.

The insoluble solid was collected, washed with water and dried (0.5 g), which was chromatographed over alumina in dichloromethane to give 0.18 g (12.0 %) of IIa as colorless needless, mp 260° and 0.20 g (13.3%) of Ia as pale yellow needles, mp 211°. *Anal.* Calcd. for $C_{12}H_{12}O_2N_4S_2$: C, 46.71; H, 3.92; N, 18.16. Found: Ia; C, 46.14; H, 4.03; N, 18.45. IIa; C, 46.77; H, 4.08; N, 18.35.

On the other hand, the aq. alkaline solution was filtered, acidified with concd. hydrochloric acid. Precipitated solid was collected and dried (0.7 g). The crude product was treated with 5% sodium hydroxide solution. The insoluble sodium salt was removed by filtration and dissolved in water, acidified with concd. hydrochloric acid to precipitate a white solid of IIb 0.2 g (16%), mp>300°. IR ν_{max}^{KBr} cm^{-1}: 3170—2920 (>NH, broad), 1595 (>C=O, broad). *Anal.* Calcd. for $C_8H_4O_2N_4S_2$: C, 38.13; H, 1.60; N, 22.23. Found: C, 38.29; H, 1.84; N, 21.98. The aq. alkaline solution was acidified with concd. hydrochloric acid to give a white solid of Ib, 0.3 g (24%), mp>300°. IR ν_{max}^{KBr} cm^{-1}: 3150—2900 (>NH, broad), 1580 (>C=O, broad). *Anal.* Calcd. for $C_8H_4O_2N_4S_2$: C, 38.13; H, 1.60; N, 22.23. Found: C, 38.33; H, 1.84; N, 22.00.

7) R. Huisgen and V.W. Eberndrofer, *Experientia*, **17**, 566 (1951).
8) K. Kaji and H. Nagashima, Unpublished.
9) 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 measured on Japan Electron Optics Lab. C-60 spectrometer with tetramethylsilane (TMS) as an internal standard.

The Formation of Dipyridazo[3,4-*b*:3′,4′-*e*]-1,4-dithiin-4,9(1*H*,6*H*)-dione (Ib) from 3-Chloro-4-mercapto-5-hydroxypyridazine (2)——2 (0.4 g) was heated under reflux in abs. ethanol (50 ml) for 5 hours. The reaction mixture was concentrated to dryness *in vacuo*. To the residue was added 5% sodium hydroxide solution and acidified with concd. hydrochloric acid to precipitate a solid, which was collected, washed with water and dried. 0.2 g of Ib (64.5%). This compound was identical with that, obtained from **1** by IR and UV spectral comparison.

The Formation of Ib from Ia——Ia (0.36 g) was heated under reflux with 47% hydrobromic acid (10 ml) for 1 hour. The reaction mixture was concentrated to dryness *in vacuo*. To the residue was added water. Precipitated solid was collected, washed with water. The crude product was dissolved in dil. sodium hydroxide solution, filtered and acidified with concd. hydrochloric acid to give 0.21 g (70.0%) of Ib. This compound was identical with an authentic sample by IR and UV spectral comparison.

The Formation of Dipyridazo[3,4-*b*:4′,3′-*e*]-1,4-dithiin-4,6(1*H*,9*H*)-dione (IIb) from IIa——IIa (0.36 g) was allowed to react with 47% hydrobromic acid (10 ml) as described above to give 0.16 g (55.3%) of IIb as white solid, mp>300°. This compound was identical with that obtained from **1** by IR and UV spectral comparison.

The Concurrent Formation of 4,9-Dichlorodipyridazo[3,4-*b*:3′,4′-*e*]-1,4-dithiin (Ic) and 4,6-Dichlorodipyridazo[3,4-*b*:4′,3′-*e*]-1,4-dithiin (IIc) from 3,5-Dichloro-4-mercaptopyridazine (3)——3 (1.8 g) was heated under reflux in abs. ethanol (50 ml) for 3 hours. The reaction mixture was concentrated to dryness *in vacuo*. To the residue was added dil. sodium hydroxide solution. Insoluble solid was collected, washed with water and dried, which was chromatographed over silica gel in dichloromethane to give a trace of If and IIf, respectively. This compound was identical with an authentic sample, respectively, by mixed melting point tests and *Rf* value of TLC.

The Formation of 4,9-Dichlorodipyridazo[3,4-*b*:3′,4′-*e*]-1,4-dithiin (Ic)——Ib (0.2 g) was warmed with phosphorus oxychloride (5 ml) for 30 minutes. The reaction mixture was poured onto cracked ice. Precipitated solid was extracted fully with dichloromethane. The dichloromethane solution was washed with water and dried over anhydrous sodium sulfate. The residue, obtained by concentration of dichloromethane was recrystallized from benzene to give 0.15 g (65.2%) of Ic as almost colorless needles, mp 275° (decomp.). *Anal.* Calcd. for $C_8H_2N_4S_2Cl_2$: C, 33.23; H, 0.69; N, 19.38. Found: C, 33.62; H, 0.89; N, 19.07.

The Formation of 4,6-Dichlorodipyridazo[3,4-*b*:4′,3′-*e*]-1,4-dithiin (IIc)——IIb (0.20 g) was allowed to react with phosphorus oxychloride (5 ml) as described above to obtain 0.17 g (73.2%) of IIc as pale yellow needles, mp 307° (decomp.). *Anal.* Calcd. for $C_8H_2N_4S_2Cl_2$: C, 33.23; H, 0.69; N, 19.38. Found: C, 33.65; H, 0.89; N, 19.21.

The Concurrent Formation of 4,9-Dibenzylthiodipyridazo[3,4-*b*:3′,4′-*e*]-1,4-dithiin (Id) and 4,6-Dibenzylthiodipyridazo[3,4-*b*:4,3-*e*]-1,4-dithiin (IId) from 3-Chloro-4-mercapto-5-benzylthiopyridazine (4)——4 (1.0 g) was heated in abs. isopropanaol (50 ml) under pressure at 100° for 10 hours. The reaction mixture was concentrated to dryness *in vacuo*. To the residue was added dichloromethane. The dichloromethane solution was washed with dil. sodium hydroxide solution, then with water and dried over anhydrous sodium sulfate. The residue, obtained by concentration of dichloromethane, was chloromatographed over silica gel to 0.2 g (23.3%) of IId as red crystals (benzene and cyclohexane), mp 250—252° and 0.25 g (29.0%) of Id as yellow crystals (benzene and cyclohexane), mp 230°. *Anal.* Calcd. for $C_{22}H_{16}N_4S_4$: C, 56.86; H, 3.46; N, 12.06. Found: Id; C, 56.89; H, 3.48; N, 11.84. IId; C, 57.10; H, 3.52; N, 11.89.

The Formation of Id from Ic——Ic (0.2 g) was allowed to stirr with sodium benzylmercaptide solution, containing benzylmercaptan (0.18 g) in 5% sodium hydroxide solution (5ml) and ethanol (5 ml) at room temperature for 5 hours. Precipitated solid was collected, washed with water and dried, which was purified by using chromatography over silica gel in dichloromethane to give 0.06 g (22.2%) of Id. This compound was identical with that obtained from 4 by mixed melting point tests and *Rf* value of TLC.

The Formation of IId from IIc——IIc (0.2 g) was allowed to react with sodium benzylmercaptide solution similarly as described above to give 0.05 g (18.5%) of IId. This compound was identical with that obtained from **4** by mixed melting point tests and *Rf* value of TLC.

The Concurrent Formation of 4,9-Dimorpholinodipyridazo[3,4-*b*:3′,4′-*e*]-1,4-dithiin (Ie) and 4,6-Dimorpholinodipyridazo[3,4-*b*:4′,3′-*e*]-1,4-dithiin (IIe) from 3-Chloro-4-mercapto-5-morpholinopyridazine (5)——**5** (1.38 g) was heated under reflux in abs. ethanol (10 ml) for 3 hours. The reaction mixture was concentrated to dryness *in vacuo*. To the residue was added dichloromethane. The dichloromethane solution was washed with dil. sodium hydroxide solution, then with water and dried over anhydrous sodium sulfate. The residue obtained by concentration of dichloromethane, was chromatographed over alumina in dichloromethane to give 0.44 g (37.9%) of Ie as colorless needles (ethanol), mp 267—268° and 0.30 g (25.8%) of IIe as colorless needles (ethanol), mp 291°. *Anal.* Calcd. for $C_{16}H_{18}O_2N_6S_2$: C, 49.21; H, 4.64; N, 21.52. Found: Ie; C, 49.37; H, 4.87; N, 21.31. IIe; C, 49.05; H, 4.81; N, 21.15.

The Formation of Ie from Ic——Ic (0.20 g) was warmed with morpholine (0.3 g) in abs. ethanol (5 ml) at *ca.* 50° for 3 hours. On cooling, precipitated solid was collected, washed with water and recrystallized from ethanol to give 0.18 g(66.7%) of Ie. This compound was identical with that from **5** in all respects.

The Formation of IIe from IIc——IIc (0.2 g) was allowed to react with morpholine similarly as described above to give 0.12 g (44.4%) of IIe. This compound was identical with that obtained from **5**, in all respects.

The Concurrent Formation of Two Pairs of Dipyridazo[4,5-*b*:4′,5′-*e*]-1,4-dithiin-1,6(2*H*,7*H*)-dithione (IV_0) and Dipyridazo[4,5-*b*:4′,5′-*e*]-1,4-dithiin-1,9(2*H*,8*H*)-dithione (V_0), and Dipyridazo[3,4-*b*:4′,5′-*e*]-1,4-dithiin-4,9(1*H*,8*H*)-dithione (VI_0) and Dipyridazo[3,4-*b*:4′,5′-*e*]-1,4-dithiin-4,6(1*H*,7*H*)-dithione (VII_0) from 3-Chloro-4,5-dimercaptopyridazine (6)——**6** (1.78 g) was heated under reflux in abs. ethanol (100 ml) for 5 hours. The reaction mixture was concentrated to dryness *in vacuo*. To the residue was added dil. sodium hydroxide solution. The aq. alkaline solution was filtered, acidified with concd. hydrochloric acid to precipitate a reddish solid, which was collected, washed with water and dried (1.0 g). This crude product was benzylated with benzylchloride (0.9 g) in ethanolic sodium hydroxide solution to separate by chromatography over silica gel in dichloromethane to give 0.30 g (18.8%) of IV as yellow needles (ethanol) mp 178°, 0.15 g (9.3%) of V as colorless needles (ethanol) ,mp 170° and 0.09 g (5.6%) of VI as colorless plates (ethanol), mp 168°, 0.18 g (11.3%) of VII as yellow needles (ethanol), mp 210°. The both compounds, IV and V were identical with an authentic sample, respectively. *Anal.* Calcd. for $C_{22}H_{16}N_4S_4$: C, 56.86; H, 3.46; N, 12.06. Found: VI; C, 56.83; H, 3.56; N, 11.98. VII; C, 56.98; H, 3.51; N, 12.03.

3-Chloro-4-mercapto-5-ethoxypyridazine (1)——**7** (7.0 g) was allowed to stand with 70% sodium hydrosulfide (9.2 g) in DMF (50 ml) at room temperature for 10 minutes. The reaction mixture was diluted with water and acidified with concd. hydrochloric acid to pH=1 and cooled in a refrigerator for 3 hours. Deposited solid was collected, washed with water and dissolved in dil. sodium hydroxide solution. The aq. alkaline solution was filtered. The filtrate was acidified with concd. hydrochloric acid to precipitate a solid, which was collected, washed with water and recrystallized from benzene to give 5.0 g (73.5%) of needles, mp 139° (decomp.). *Anal.* Calcd. for $C_6H_7ON_2SCl$: C, 37.83; H, 3.70; N, 14.71. Found: C, 37.61; H, 3.81; N, 14.85.

3-Chloro-4-mercapto-5-hydroxypyridazine (2)——a) From **1**: **1** (1.9 g) was heated under reflux in 10% sodium hydroxide solution (12 ml) and ethanol (12 ml) for 1 hour. The reaction mixture was concentrated to almost dryness *in vacuo*. To the residue was added water and acidified with concd. hydrochloric acid to precipitate a solid, which was collected, washed with water, dried and recrystallized from benzene to give 1.0 g (62%) of 2 as pale green crystals, mp 132° (decomp.). *Anal.* Calcd. for $C_4H_3ON_2SCl$: C, 29.51; H, 1.86; N, 17.23. Found: C, 29.55; H, 1.93; N, 16.94.

b) From **8**: To a solution of anhydrous aluminium chloride (1.45 g) in dry-toluene (25 ml) was added **8** (1.4 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, washed with water and dried, which was recrystallized from benzene to give 0.6 g (75%) of **2**. This compound was identical with that obtained from **1** in all respects.

3,5-Dichloro-4-mercaptopyridazine (3)——**14** (1.8 g) was allowed to react with anhydrous aluminium chloride (1.0 g) in dry-toluene (30 ml) similarly as described above to give 0.8 g (66.7%) of 3 as yellow plates, mp 119° (decomp.). *Anal.* Calcd. for $C_4H_2N_2SCl_2$: C, 26.53; H, 1.11; N, 15.47. Found: C, 26.26; H, 1.21; N, 15.27.

3-Chloro-4-mercapto-5-morpholinopyridazine (5)——**10** (3.5 g) was stirred with 70% sodium hydrosulfide (4.8 g) in ethanol (50 ml) at room temperature for 3 hours. The reaction mixture was concentrated to almost dryness *in vacuo*. To the residue was added water and acidified with concd. hydrochloric acid to precipitate a solid, which was collected, dissolved in dil. sodium hydroxide solution and filtered. The filtrate was acidified with concd. hydrochloric acid to pH=1. Deposited solid was collected, washed with water and dried to give 2.5 g (71%) of **5** as yellow solid, mp 155° (decomp.). *Anal.* Calcd. for $C_8H_{10}ON_3SCl$: C, 41.40; H, 4.35; N, 18.12. Found: C, 41.57; H, 4.55; N, 17.79.

3-Chloro-4,5-dimercaptopyridazine (6)——**15** (3.6 g) was allowed to react with anhydrous aluminium chloride (2.9 g) in dry-toluene (50 ml) similarly as described above to give 1.2 g (66.7%) of **6** as reddish solid, mp 148° (decomp.). *Anal.* Calcd. for $C_4H_3N_2S_2Cl$: C, 26.89; H, 1.69; N, 15.68. Found: C, 26.78; H, 1.72; N, 15.40.

3-Chloro-4-benzylthio-5-ethoxypyridazine (8)——**1** (3.8 g) was allowed to stirr with benzylchloride (2.8 g) in 5% sodium hydroxide solution (80 ml) and ethanol (80 ml) at room temperature for 1 hour. Precipitated solid was collected, washed with water and recrystallized from cyclohexane to give 3.0 g (52.0%) of **8** as colorless needles, mp 101°. *Anal.* Calcd. for $C_{13}H_{13}ON_2SCl$: C, 55.62; H, 4.67; N, 10.00. Found: C, 55.87; H, 4.90; N, 9.92.

3-Chloro-4-benzylthio-5-hydroxypyridazine (11)——**8** (2.0 g) was heated under reflux in 20% sodium hydroxide solution (50 ml) and ethanol (50 ml) for 30 minutes. 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 pH=1. Deposited solid was collected, washed with water and recrystallized from benzene to give 1.1 g (64.1%) of **11** as colorless crytals, mp 142°. *Anal.* Calcd. for $C_{11}H_9ON_2SCl$: C, 52.21; H, 3.56; N, 11.08. Found: C, 52.35; H, 3.51; N, 10.97.

4-Benzylthio-5-chloro-3(2*H*)-pyridazinone (13)——**12**[6] (1.6 g) was allowed to react with benzylchloride (1.5 g) in ethanolic sodium hydroxide solution similarly as described above to give 1.5 g (60.0%) of **13** as colorless needles (ethanol), mp 139°. *Anal.* Calcd. for $C_{11}H_9ON_2SCl$: C, 52.42; H, 3.60; N, 11.12. Found: C, 52.67; H, 3.83; N, 10.97.

3,5-Dichloro-4-benzylthiopyridazine (14)——a) From **11** : **11** (2.5 g) was allowed to react with phosphorus oxychloride (10 ml) at room temperature similarly as described above to give 1.1 g (42%) of **14** as pale yellow plates (petroleum ether), mp 45—46°. *Anal.* Calcd. for C, 48.72; H, 2.97; N, 10.33. Found: C, 48.98; H, 3.06; N, 10.42.

b) From **13** : **13** (2.5 g) was allowed to warm with phosphorus oxychloride (10 ml) similarly as described above to obtain 1.8 g (67%) of **14**. This compound was identical with that obtained from **11** by mixed melting point tests and *Rf* value of TLC.

Acknowledgement The authors are grateful to Dr. J. Iwao, Mr. Yamazaki, Dr. T. Okuda and Dr. K. Kodera of Tanabe Pharmaceutical Co., Ltd. for NMR and mass spectra measurement. Elemental analyses were carried out by Miss F. Kawamura to whom the author's thanks are due. Thanks are also given to Miss N. Takasu and Mr. T. Ikami for their assistances in the experimental work.