The Synthesis of Sulfur-Containing Pyridazines. I. Benzylthiolation with a Subsequent Selective Debenzylation on 4,5-Dihalo-3-Pyridazones.

Kenji Kaji[1], **Hiroshi Mori**[2], **Iehisa Yoshida, Takako Ichii, Hiromu Nagashima** (*Gifu College of Pharmacy**1) **and Raymond N. Castle** (*Univercity of New Mexico**2)

Treatment of 4,5-dichloro- (I) or 4,5-dibromo-3-pyridazone (I′) with sodium benzylthiolate or benzylisothiuronium chloride in aqueous alkaline alcoholic solution gives 4, 5-bis-(benzylthio)-3-pyridazone (II*a*) in a reasonable yield. However, I is allowed to react with an excess of sodium benzylthiolate in the presence of sodium amide in dry toluene, by heating them under reflux for ten hours, to yield 4-mercapto-5-benzylthio-3-pyridazone (III*a*) as a by-product, together with the main product, II*a*. Similar results are observed in the reactions of I′ with sodium benzylthiolate, with sodium 2-furfurylthiolate, and with 2-thenylthiolate, yielding III*a*, 4-mercapto-5-(2-furfurylthio)-(III*b*), and 4-mercapto-5-(2-thenylthio)-3-pyridazone (III*c*), respectively, besides the main products, corresponding 4,5-bis(benzylthio)-3-pyridazones under the similar reaction conditions. The courses of these reactions are confirmed by independent experiments and the structures of the products are established by unambiguous methods.

During the course of the study on the synthesis of sulfur-containing pyridazine derivative[3], the present paper deals with an interesting result obtained from a reaction of 4.5-dihalo-3-pyridazone with an excess of sodium benzylthiolate or analogous reagents in the presence of sodium amide in dry toluene, by heating them under reflux for 10 hours, in attempts to prepare a series of 4,5-bis(benzylthio)-3-pyridazones.

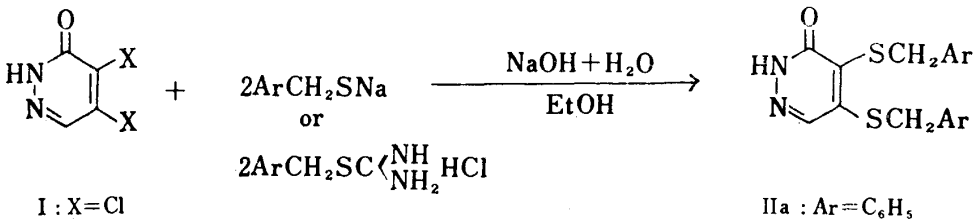
General procedure for preparation of this type of compounds, such as 4,5-bis(benzylthio)-3-pyridazone (II*a*), 4.5-bis(2-furfurrythio)-3-pyridazone[4] (II*b*), and 4.5-bis(2-thenylthio)-3-pyridazone[4] (II*c*), may be classified as follows: (1) Bennylthiolation or arylmethylthiolation of 4,5-dihalo-3-pyridazones (I : X=Cl and I′ : X=Br) in basic media; (2) Benzylation or arylmethylation of 4,5-dimercapto-3-pyridazone in basic media; (3) Stepwise method composed of procedure 1 and 2, for example, I or I′ is coverted to 4-halo-5-mercapto-3-pyridazone (IV : X=Cl or IV′ : X=Br) or 4-halo-5-benzylthiopyridazone (V*a* : X=Cl, Ar=C_6H_5-; V*a*′ : X=Br, Ar=C_6H_5-; V*b* : X=Cl, Ar=2-C_4H_3O-; or V*c* : =Cl, Ar=2-C_4H_3S-) from which directly or via 4-mercapto-5-benzythio-3-pyridazon (III*a* : Ar=C_6H_5-; III*b* : Ar=2-C_4H_3O-; or III*c*:

*1. 492-36, Mitahora, Gifu, JAPAN

*2. Department of Chemistry, University of New Mexico, Albuquerque, New Mexico, U. S. A.

Ar=2-C_4H_3S-), the purpose compound (II*a*, II*b* or II*c*) is producible.

4. 5-Dichloro-3-pyridazone reacted with sodium benzylthiolate or benzylisothiuronium chloride in aqueous alkaline ethanolic solution, by heating them for a few hours, to give 4. 5-bis(benzylthio)-3-pyridazone (II*a*) in a good yield and almost similar results were observed in the preparation of the II*b* and II*c*, in such a reaction condition. (Eqn. 1 and TABLE 1)



(1)

I : X=Cl

I′: X=Br

IIa : Ar=C_6H_5

IIb : Ar=2-C_4H_3O

IIc : Ar=2-C_4H_3S

The reaction is formulated as the equation 1 and the products are shown in the TABLE 1.

TABLE 1 4, 5-Bis(benzylthio)-3-pyridazones

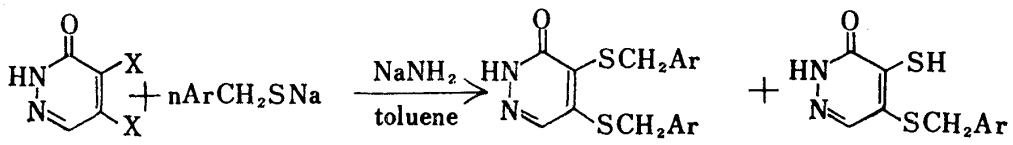
Comd. No.	Ar	M.P., °C*	Yield, %	Formula	Analysis Calcd. C	Calcd. H	Calcd. N	Found. C	Found. H	Found. N
II*a*	C_6H_5	160	94.0	$C_{18}H_{16}ON_2S_2$	63.32	4.74	8.23	63.63	4.73	8.59
II*a*			92.0					63.48	4.72	8.40
II*b*	2-C_4H_3O	97	43.8	$C_{14}H_{12}O_3N_2S_2$	52.32	3.68	8.72	52.42	3.97	9.17
II*c*	2-C_4H_3S	121	86.1	$C_{14}H_{12}ON_2S_4$	47.69	3.43	7.94	47.96	3.60	8.34

* All melting points are uncorrected.

On the contrary, I reacted with an excess of sodium benzylthiolate (R) (I : R = 1 : 4 (molar ratio) or two equivalents of R required by I) in the presence of sodium amide in dry toluene, by heating them under reflux for ten hours, to produce 4(or 5)-mercapto-5(or 4)-benzylthio-3-pyridazone, (III*a*), (m.p., 186°, yield, 20%) together with the main product, II*a*, (m.p., 160°, yield, 48.5%). And almost similar results were also noticed as expected in the cases in which I′ and an excess of R, and analogous reagents, were allowed to react in a similar reaction condition as above; viz., the by-products were III*a* (yield, 18%), 4-(or 5)-mercapto-5(or 4)-(2-furfurylthio)-3-pyridazone, (III*b*), (m.p., 145°, yield, 19%) and 4(or 5)-mercapto-5(or 4)-(2-thenylthio)-3-pyridazone, (III*c*), (m.p., 153, °yield, 5.9%), corresponding to the main porducts II*a*, II*b* (m.p., 97°, yield, 40.6%), and II*c* (m.p., 121°, yield, 71.8%).

The reaction is expressed in the eqation 2 and the results are shown in the TABLE 2.

Each of III type compounds, easily converted by benzylation to the crresponding II, appears in greenish yellow crystals and shows the characteristic frequencies, ν_{S-H} in 2500 cm^{-1} and $\nu_{C=O}$ in a region of 1620 (III*a*), and 1630 cm^{-1} (III*b* and III*c*), in I.R. absorption spectra. On the contrary, all II type compounds are almost colorless in pure states, and similar in $\nu_{C=O}$ in 1630cm^{-1} to, however, different in lack of the



(2)

IIa : Ar=C_6H_5 IIIa : Ar=C_6H_5

IIb : Ar=2-C_4H_3O IIIb : Ar=2-C_4H_3O

IIc : Ar=2-C_4H_3S IIIc : Ar=2-C_4H_3S

TABLE 2. Products from a reaction of 4,5-Dihalo-3-Pyridazone with an excess of Sodium Benzylthiolate in the prosence of sodiun amide in dry toluene (Eqn 2)

Exp. No.	4(or 5)-Mercapto-5(or 4)-benzylthio-3-pyridazone					Analysis						4,5-Bis(benzylthio)-3-pyridazone			Total Yield, %
	Compd. No.	Ar	M.P., °C*	Yield, %	Formula	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N	Compd. No.	M.P., °C	Yield, %	
1	IIIa	C_6H_5	186	20.0	$C_{11}H_{10}ON_2S_2$	52.77	4.03	11.19	52.81	4.01	11.03	IIa	160	48.5	68.5
2	IIIa	C_6H_5		18.0					52.83	4.01	11.20	IIa	160	59.0	77.0
3	IIIb	2-C_4H_3O	145	19.0	$C_9H_8O_2N_2S_2$	44.98	3.36	11.65	44.85	3.46	11.62	IIb	97	40.6	59.0
4	IIIc	2-C_4H_3S	153	5.9	$C_9H_8ON_2S_3$	42.62	3.15	10.93	42.40	3.45	11.02	IIc	121	71.8	77.7

* All melting points are uncorrected.

characteristic frequency in 2500cm^{-1} from, the III type ones.

Although it was experimentally revealed that the III type compound, partly debenzylated product always formed together with the II type compound, under the reaction condition as mentioned above, it is still difficult to say directly about the structure the II type compound or the reaction mechanism. For all that, the formation of the mercaptans by C—S bond cleavage of benzyl-, other aralkyl- or alkylthio compounds, by using sodium in liquid ammonia,[5] lithium in demethylamine,[6] aluminium tribromide,[7] or aluminium trichloride, in toluene,[8] has been well known.

In the circumstances, prior to a direct structural proof of the III type compound, on the assumption that the compound III, should be assignable to 4-mercapto-5-benzylthio-3-pyridazone (IIIi), a stepwise method of preparing the compounds, III$_i$ and II, as shown in the Chart 1, was attempted to carry out. In the chart, the compounds(IV or IV′), and(Vi), are written postulationally, likewise IIIi, as 4-halo-5-mercapto- and 4-halo-5-benzylthio-3-pyridazone, respectively.

Following the scheme in the chart 1, the three kinds of the compounds IIIi were prepared by thiolation of the corresponding Xi (4-chloro-5-benzylthio-(m.p., 197°), 4-bromo-5-benzylthio-(m.p., 197°), 4-chloro-(2-furfurylthio)-(m.p., 133°), or 4-chloro-(2-thenylthio) -3-pyridazone (m.p., 170°)) with sodium hydrosulfide, by heating them in aqueous ethanolic solution, and any one of IIIi's compounds proved identical in any respect with the corresponding compound (III$_a$, III$_b$, or III$_c$) formed as by-product in the reaction 2.

In the course of preparing four kinds of the Vi type compound, all of them were easily formed by direct benzylthiolation of I (or I′) in a rather moderate reaction condition, or a short time contact of I (or I′)

with the corresponding soldium benzylthiolate in aqueous alkaline ethanolic solution at room temperature, and they were also prepared by S-benzylation of the IV or IV′, in a similar moderate condition as mentioned (TABLE 4).

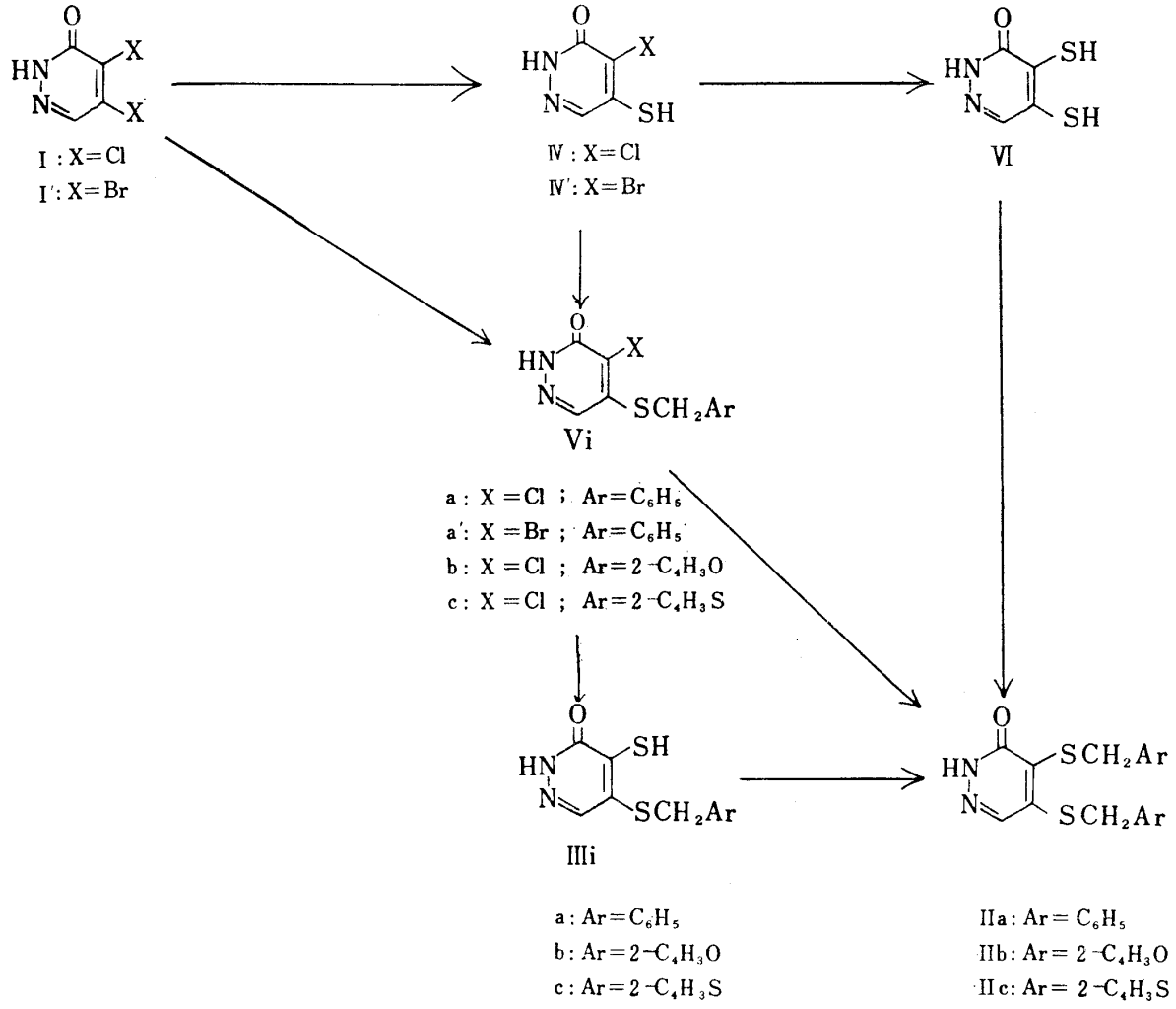


chart 1

The compound IV, or IV′, one of the most important key compounds in the scheme, derived from I or I′, respectively, by thiolation with sodium hydrosulfide in aqueous ethanolic solution at a room temperature, is comparatively unstable, particulary to heat, acid or light, in the presence or absence of a polar solvent, to produce dipyridazo[4, 5-b: 4, 5-e]-1, 4-dithiin-1, 6-dione.[9,10]

Each of four kinds of the compound Vi, obtained from the IV or IV′ by benzylation, or diredly from I or I′ by appropriate benzylthiolation, was easily converted by an additional benzylthiolation to the corresponding II compound. In this connection, the compound II was also formed by di-benzylation of crude 4, 5-dimercapto-3-pyridazone (IV) derived from IV or IV′ by additional thiolation with sodium hydrosulfide in aqueous ethanolic solution, by heating them under pressure. (TABLE 5)

All of the compounds IV, IV′, and IV, show the similar characteric frequency of stretching viberation of S-H group in the region of 2500~2550cm^{-1} in the I.R. absorption spectra, likewise as in the compounds of

TABLE 3 4-Mercapto-5-benzylthio-3-pyridazones (Ⅲi)

Ar	M.P., °C*1	Nujol I.R. ν(cm⁻¹) S-H	Nujol I.R. ν(cm⁻¹) C=O	Yield, % based on the Vi
C_6H_5	186	2500	1620	75.0
C_6H_5*2				88.0
2-C_4H_3O	145	2500	1630	68.8
2-C_4H_3S	153	2500	1630	73.2

*1 All melting points are uncorrected.

*2 Bromo derivative, and in other cases chloro derivative, was used as Vi.

TABLE 4 4-Halo-5-benzylthio-3-pyridazones (Vi)

Ar	X	M.P*1., °C	Yield, % Method† A	Yield, % Method† B	Formula	Analysis, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
C_6H_5	Cl	197	27.0	41.3*2	$C_{11}H_9ON_2SCl$	52.28	3.59	11.09	52.34	3.65	11.39
C_6H_5	Br	197	28.7	45.4*2	$C_{11}H_9ON_2SBr$	44.45	3.05	9.43	44.66	3.14	9.67
2-C_4H_3O	Cl	133	37.0*2		$C_9H_7O_2N_2SCl$	44.54	2.91	11.59	44.78	3.14	12.00
2-C_4H_3S	Cl	170	23.3	60.0*2	$C_9H_7ON_2S_2Cl$	41.77	2.73	10.83	41.78	2.83	11.08

*1 All melting points are uncorrected.

*2 Analytical values shown are for the products prepared by the methods with asterisks.

† Method A : Benzylthiolation of Ⅰ or Ⅰ′. Method B : Benzylation of Ⅳ orⅣ′.

TABLE 5 Yields of 4,5-Bis(benzylthio)-3-pyridazones (Ⅱ) prepared by various methods

Ar	Yield, % Method A†	Yield, % Method B_1†	Yield, % Method B_2†
C_6H_5	69.1, 88.2*	80.0	60.0
2-C_4H_3S	63.7	35.4	70.0

* Bromo derivative, and in other cases chloro derivative, was used as starting material in Method A.

† Method A:Benyzlthislation of Vi. Method B_1:Benzylation of Ⅲi. Method B_2: Dibenzylation of Ⅵ

Ⅲ, which is rather weak in intensity but well-defined, and completely disappeared when these compounds are S-benzylated.

Subsequent to the above fact, a direct structural proof of Ⅲ$_a$ for the compound, 4-mercapto-5-benzylthio-3-pyridazone, as a representative of the Ⅲ$_i$ type compounds, was carried out as follows: The compound, $V_{i=a}$ or $V'_{i=a}$, whose structure was tentatively presumed to be 4-halo-5-benzylthio-3-pyridazone as described above, from which the compound Ⅲ$_a$ being derivable, was easily convereted to 4 (or 5)-morpholino-5(or 4)-benzylthio-3-pyridazone (m.p., 191°, yield, 79.0%) (Ⅶ), by heating under reflux with an excess

of morpholine, and this compound was desulfurized by heating with Raney-nickel in dimethylformamide to form 4-morpholino-3-pyridazone (m.p., 175°, yield, 44.2%) (Ⅷ). Structural assignment of the compound to Ⅷ is attributed to the isomerism relationship between Ⅷ and 5-moroholino-3-pyridazone (m.p., 257°) (Ⅺ) (chart 2). The structure of Ⅺ is unambiguous because this compound is derived from 4-chloro-5-morphilino- (m.p., 236°)(Ⅸ)[11] or 4-bromo-5-morpholino-3-pyridazone (m.p., 157°) (Ⅸ′)[11], as well as from 3-chloro-4-morpholino-6-pyridazone (m.p., 200°)(ⅩⅣ)[12], by catalytic dechlorination with palladium on charcoal. (chart 3)

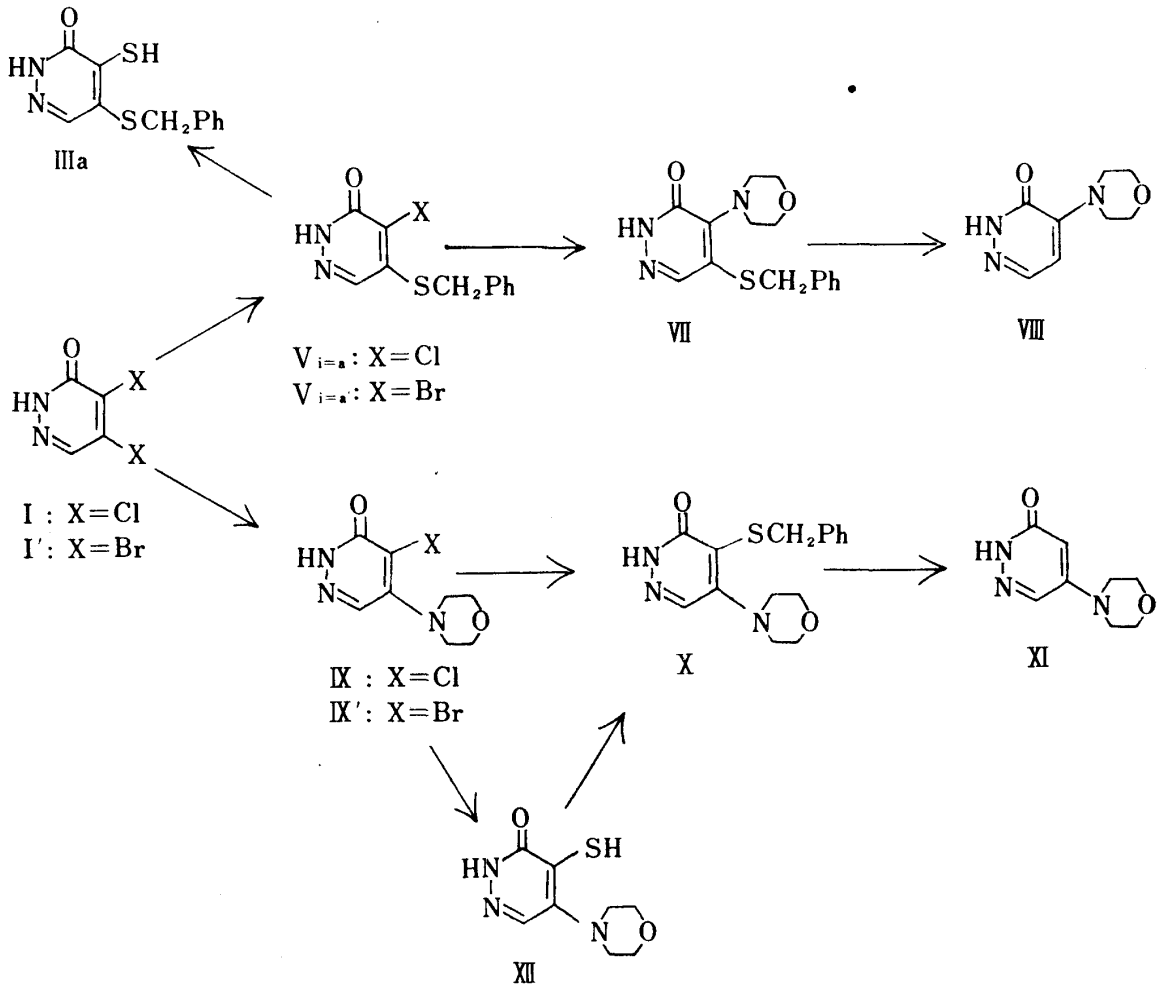


chart 2

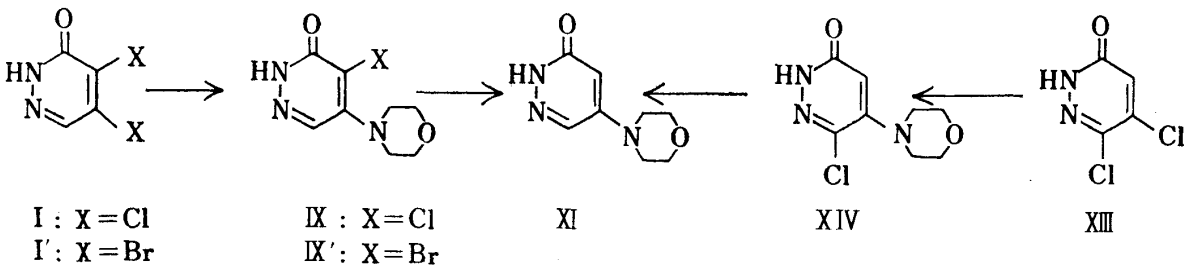


chart 3

By the way, the compound IX or XIV was prepared by heating I or 3, 4-dichloro-6-pyridazone, (XIII)[13], respectively, with morpholine in ethanol. The compound XI was also formed by desulfurization of 4-benzylthio-5-morpholino-3-pyridazone (X) (m.p., 201°) by heating with Raney-nickel in dimethylformamide, and the latter was obtained from IX or IX′, by benzylthiolation or via 4-mercapto-5-morpholino-3-pyridazone XII (m.p., 171°) derived from IX or IX′, by S-benzylation. (chart 2)

Furthermore to ascertain an isomerism relationship between the two compounds VIII and XI, each of them was converted to the same compound, 4-morpholino-pyridazine (m.p., 89°) (XVI), by way of chlorination followed by catalytic dechlorination with palladium on charcoal, viz., via 4-morpholino-3-chloropyridazine (m.p., 122°) (XV) and 5-moroholino-3-chloropyridazine (m.p., 115°) (XVII), respectively, as shown in the chart 4.

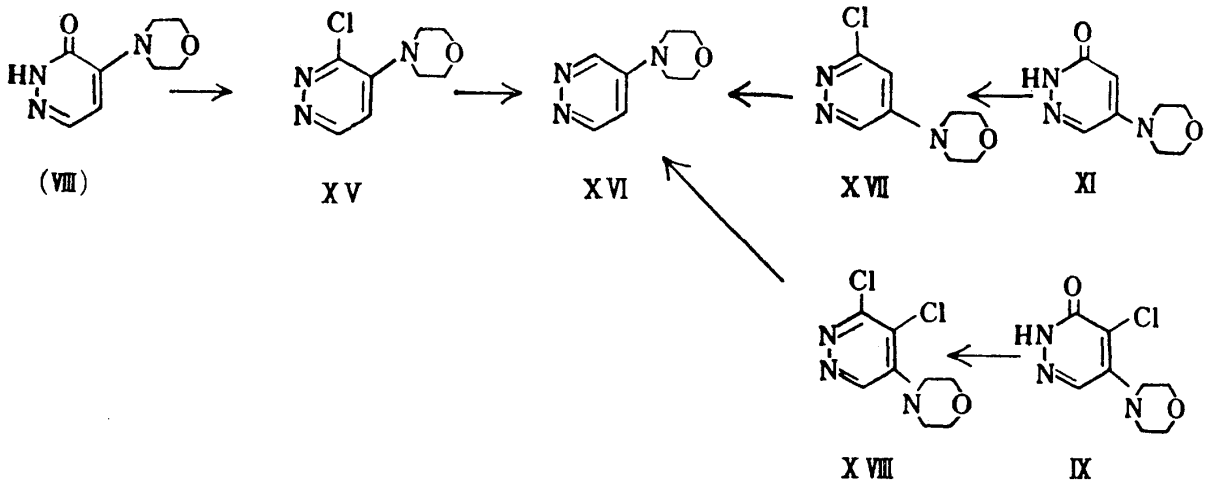
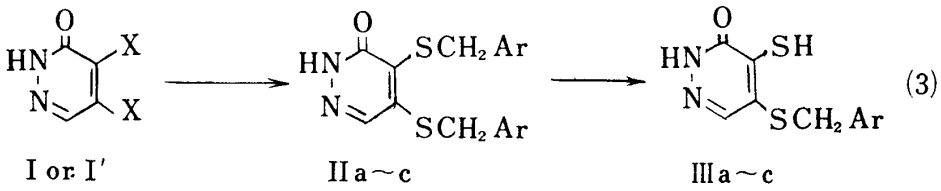


chart 4

The compound XVI, was also derived by catalytic dechlorination of 3, 4-dichloro-5-morpholino pyridazine (m.p., 107.5°) (XVIII) prepared by chlorinating IX, from which XI being derivable.

On the basis of the experimental facts mentioned hitherto, it may be reasonable to assign the compounds, IV, IV′, $V_{i=a}$, and $V'_{i=a'}$ to 4-chloro-5-mercapto-, 4-bromo-5-mercapto-, 4-chloro-5-benzylthio-, and 4-bromo-5-benzylthio-3-pyridazone, respectively, and consequently the compound IIIa to 4-mercapto-5-benzyl thio-3-pyridazone. It seems also reasonable, by analogical inference, to assume the compounds IIIb and IIIc being assignable to 4-mercapto-5-(2-furfurylthio)-3-pyridazone and 4-mercapto-5-(2-thenylthio)-3-pyridazone, respectively, and each of the compounds III$a\sim c$ formed as by-products in the reaction (Eqn. 2) being derived presumably by the selective debenzylation from the corresponding one of the compounds II$a\sim c$ initially formed in the course of the reaction.

Finally in order to confirm whether such debenzylition really occurs in the course of the reaction, IIa was subjected to the reaction with an excess of sodium benzylthiolate in a similar reaction conditionin as mentioned above, to produce IIIa, in a rather lower yield, but undoubtedly. (Eqn. 3)



I or I′ II a～c III a～c (3)

It is concluded that a reaction of 4, 5-dihalo-3-pyridazone with an excess of sodium benzylthiolate in the presence of sodium amide in dry toluene, by heating them under reflux for a rather longer time, always forms 4-mercapto-5-benzylthio-3-pyridazone together with 4, 5-bis(benzylthio)-3-pyridazone, in other words, in the course of the reaction, the benzylthiolation never fails to be followed by the debenzylation which occurs selectively on the benzylthiol group attached to the position 4, not on that to the position 5, of the pyridazone ring.

Further work is in progress on the reaction of 4, 5-and 4, 6-dihalo-N^2-substituted-3-pyridazones with sodium benzylthiolate, and will be reported at a later date.

Experimental

I. *A reaction of 4, 5-dihalo-3-pyridazone with sodium benzylthiolate in aqueous alkaline ethanolic solution.*

A. 4, 5-*Bis (benzylthio)-3-pyridazone* (II*a*)[11] —— a) 4, 5-Dichloro-3-pyridazone (0.82g) was added to sodium benzylthiolate solution containing benzylisothiuronium chloride (2.02g) in a mixture of 5% sodium hydroxide solution (20ml.) and ethanol (20ml.), and the mixture was heated under reflux for 3 hours. On cooling the resulted solution, it was acidfied with hydrochloric acid to precipitate crude 4, 5-bis(benzylthio)-3-pyridazone[11] (II*a*) (m. p. 157°, 1.7g) which was collected, washed with water and dried. Purification was effected by recrystallization from ethanol to form almost colorless crystals (m. p. 160°, 1.6g) Anal. for II*a*. (TABLE 1) I. R. cm^{-1} : $\nu_{c=0}$ 1630

b) Starting from 4, 5-dibromo-3-pyridazone (1.27g) and sodium benzylthiolate in an aqueous alkaline ethanolic solution, and treating them in a similar manner as described above, II*a* (mp. 160°, 1.56g) was obtained. Anal for II*a* (TABLE 1)

B. 4, 5-*Bis (2-furfurylthio)-3-pyridazone* (II*b*)[4] —— 4, 5-Dichloro-3-pyridazone (0.82g) was allowed to react with sodium furfurylthiolate consisted of 2-furfurylmercaptan (1.14g) in a mixture of 5% sodium hydroxide solution (20ml) and ethanol (20ml), under an almost similar condition as described on the A, to yield 4, 5-bis(2-furfurylthio)-3-pyridazone (mp. 97°, almost colorless crystals, 0.7g or 43.8% in yield). I. R. cm^{-1} : $\nu_{c=0}$ 1630. Anal. for II*b*. (TABLE 1)

C. 4, 5-*Bis(2-thenylthio)-3-pyridazone* (II*c*)[4] —— 4, 5-Dichloro-3-pyridazone (1.65g) was added to the sodium thiolate solution containing 2-thenylisothiuronium chloride (4.17g) in a mixture of 5% sodium hydroxide solution (40ml) and ethanol (40ml), and the whole was allowed to react and treated similarly as

described above. 4,5-Bis(2-thenylthio)-3-pyridazone, recrystallized from ethanol(m.p. 121°, almost colorless crystals, 3.00g or 86.1% in yield) was obtained. I.R. cm^{-1} : $\nu_{C=O}$ 1630. Anal. for IIc. (TABLE 1)

II. *A reaction of 4,5-dihalo-3-pyridazone with an excess of sodium benzylthiolate in the presence of sodium amide in dry toluene by heating them under reflux for a rather long time.*

A. *A reaction of 4,5-dichlopo-3-pyridazone with sodium benzylthiolate* a) —4,5-dichloro-3-pyridazone (3.30g) was added to sodium benzylthiolate supension in toluene previously prepared by heating benzylmercaptan (9.94g) with powdered sodium amide (3.50g) in dry toluene (200ml) for 30 minutes, and the mixture was heated under reflux for ca. 10 hours.

Reaction mixture was concentrated in a vacuum to dryness, residual solid was treated with water (70ml), and the residual solid (A) was separated by filtration from the filtrate (B). The solid (A) was suspended in water and acidified with concd. hydrochloric acid to pH=ca.1. Collected solid was washed with water, dried, and recrystallized from ethanol to give 4,5-bis(benzylthio)-3-pyridazone (3.30g or 48.5% in yield), almost colorless crystals m.p. 160°underpressed on admixture with an authentic specimen.

The alkaline filtrate (B) was acidified with concd. hydrochloric acid to precipitate a solid which was collected, washed with water, and recrystallized from ethanol to give 4-mercapto-5-benzylthio-3-pyridazone (IIIa) (1.00g or 20.0% in yield), greenish yellow crystals, m.p. 186° undepressed by admixture with the compound (m.p., 186°) derived from 4-chloro-5-benzylthio-3-pyridazone ($V_{i=a}$). I.R. cm^{-1} : $\nu_{C=O}$ 1620; ν_{S-H} 2500. Anal. for IIIa. (TABLE 2)

b) The two componds, 4,5-bis(benzylthio)-3-pyridazone (m.p., 160°, 2.00g or 59.0% in yeild) and 4-mercapto-5-benzylthio-3-pyridazone (m.p., 186°, 0.45g or 18% in yield) were obtained, starting from 4,5-dibromo-3-pyridazone (2.53g) by a similar treatment as described on the Method II, A-a.

B. *Reaction of 4,5-dibromo-3-pyridazone with sodium 2-furfurylthiolate* —— *4,5-Bis(2-furfurylthio)-3-pyridazone* (IIb) (m.p., 97°, 7.80g or 40.6% in yield) and *4-mercapto-5-(2-furfurylthio)-3-pyridazone* (IIIb) (m.p. 145°, greenish-yellow crystals, 2.70g or 19.1% in yield) were obtained by treatment of 4,5-dibromo-3-pyridazone (15.24g) with the sodium thiolate suspension, prepared from 2-furfurylmercaptan (27.36g) and sodium amide (10.50g) in dry toluene (600ml), similarly as described on the Method II, A-a.

Anal. Calcd. for $C_{14}H_{12}O_3N_2S_2$ (320.388): C, 52.32; H, 3.68; N, 8.72. Found: C, 52.40; H, 3.72; N, 8.83 M.p., 97° (IIb) was undepressed on admixture with a sample prepared by the Method I-A. IR for IIb cm^{-1} : $\nu_{C=O}$ 1630.

Anal. for IIIb (TEABLE 2) M.p. 145° (IIIb) was undepressed admixture with a sample derived from 4-chloro-5-(2-furfurylthio)-3-pyridazone ($V_{i=b}$). I.R. for IIIb cm^{-1} : $\nu_{C=O}$ 1630, ν_{S-H} 2500.

C. *Reaction of 4,5-dibromo-3-pyridazone with sodium 2-thenylthiolate* —— *4,5-Bis (2-thenylthio)-3-pyridozone* (IIc) (m.p., 121°, 5.10g or 71.8% in yield) and *4-mercapto-5-(2-thenylthio)-3-pyridazone* (IIIc) (m.p., 153°, greenish-yellow crystals, 0.30g or 5.9% in yield), were obtained by treating 4,5-dibromo-3-pyridazone (5.08g) with the sodium thiolate, prepared from 2-thenylmercaptan (10.40g) and sodium amide (3.50) in dry toluene (200ml), similarly as described on the Method II-A.

Anal. Calcd. for $C_{14}H_{12}ON_2S_4$ (352.516) : C, 47.69; H, 3.43; N, 7.94. Found : C, 47.73; H, 3.63; N, 8.10 m. p. 121°C (IIIc) showed no depression on admixture with a sample prepared by the Method I-C. I. R. for IIc cm^{-1} : $\nu_{C=O}$ 1630.

Anal. for IIIc (TABLE 2) M. p. 153° (IIIc) was undepressed on admixture with a sample prepared from 4-chloro-5-(2-thenylthio)-3-pyridazone (Vi=c). I. R. for IIIc cm^{-1} : $\nu_{C=O}$ 1630; ν_{S-H} 2500.

III. *A reaction of* 4, 5-*dihalo*-3-*pyridazone with sodium hydrosulfide in ethanol at a room temperature.*

A. 4-*Chloro*-5-*mercapto*-3-*pypidazone* (IV) —— 4, 5-Dichloro-3-pyridazone (8.25g) was added to the solution containing 32% aq. sodium hydrosulfide solution (26.3g) in ethanol (50ml), and the whole was stirred at a room temperature. Spontaneous evolution of heat was noticed, while stirring deposited sodium chloride increased the amount and stirring was continued for 2 hr.

Reaction mixture was filtered to remove deposited salt, the filtrate (yellow sol.) was concentrated in a vacuum, the residue was dissolved in water (50ml.) and acidified with concentrated hydrochloric acid (ca. 12ml.) to pH=ca. 1 to precipitate the product which was collected, washed with a small amount of water and dried in a vacuum desiccator. Crude 4-chloro-5-mercapto-3-pyridazone (m. p. >300° and almost colorless crystals) amounted 6.8g. (83.6% in yield). Purification was effected by alternate dissolving in an alkaline solution and precipitating by acidification with concentrated hydrochloric acid.

Anal. Calcd. for $C_4H_3ON_2SCl$ (162.603): C, 29.54; H, 1.86; N, 17.23: Found. C, 29.84; H, 1.93; N, 17.41. I. R. cm^{-1} : ν_{S-H} 2550 and $\nu_{C=O}$ 1650

B. 4-*Bromo*-5-*mercapto*-3-*pyridazone* (IV′) —— This compound (m. p. > 300° and almost colorless crystals, 8.6g or 84.1% in yield) was obtained, starting from 4, 5-dibromo-3-pyridazone (12.7g.) by treating sinilary as described above.

Anal. Calcd. for $C_4H_3ON_2SBr$ (207.066): C, 23.40; H, 1.47; N, 12.53. Found: C, 23.56; H, 1.37; N, 13.76. I. R. cm^{-1} : ν_{S-H} 2550 and $\nu_{C=O}$ 1650.

IV. 4-*Halo*-5-(*benzylthio*)-3-*pyridazones* (Vi)

A. 4-*Halo*-5-*benzylthio*-3-*pyridazone* (Vi=a and Vi=a′) —— a) 4, 5-Dichloro-3-pyridazone (3.3g.) was dissolved in an alkaline solution consisted of 5% sodium hydroxide sol. (80ml.) and concd. aq. ammonia (64ml.) and to the solution benzylmercaptan (4.97g.) in ethanol (150ml.) was added. The mixture was stirred at a room temporature for 2 hr.

Reaction mixture was acidified with a mixed acid (glacial acetic acid and concd. hydrochloric acid) and concentrated in a vacuum. Precipitated solid was collected, washed with water, and dried. Dried material was recrystallized twice from ethanol to give 4-*chloro*-5-*benzylthio*-3-*pyridazone* (m. p. 191-193°, 1.4g. or 27.0 % in yield) (Vi=a). Further purification was effected by recrystallization again from ethanol to yield an analytical specimen, m. p. 197°, unchanged by admixture with a sample prepared by the method IV, A-b.

Anal. Calcd. for $C_{11}H_9ON_2SCl$ (252.721): C, 52.28; H, 3.59; N, 11.09. Found: C, 52.23; H, 3.75; N, 11.31.

b) Benzyl chloride (7.54g.) was added to the sodium thiolate solution containing 4-chloro-5-mercapto-3-pyridazone (7.80g.) (IV) in a mixture of 5% sodium hydroxide sol. (93ml.), concd. aq. ammonia (90ml.)

and ethanol (183ml.) and the whole was stirred at a room temperature for 2 hr.

Reaction mixture was filtered and an alkaline filtrate was treated almost similarly as the Method Ⅳ A-a to give 4-*chloro*-5-*benzylthio*-3-*pyridazone* (m. p. 193-194°, 5.0g, or 41.3% in yield) ($V_{i=a}$). Analytical specimen melted at 197° (from ethanol) and mixed m. p. by admixture with a sample prepared by the Method Ⅳ, A-a was unchanged. Anal. for this product. (TABLE 4).

a′) 4-*Bromo*-5-*benzylthio*-3-*pyridazone* (m. p. 197°, 1.7g. or 28.7% in yield) ($V_{i=a'}$) was obtained by benzylthiolation of 4, 5-dibromo-3-pyridazone (5.8g) with sodium benzylthiolate solution (benzylmercaptan, 4.97g.) in a similar manner as described on the Method Ⅳ, A-a. Mixed m. p. on admixture with a sample prepared by the Method Ⅳ, A-b′ was 197°.

b′) 4-*Bromo*-5-*benzylthio*-3-*pyridazone* (m. p. 197°, 2.7g. or 45.4% in yield) ($V_{i=a'}$) was obtained by benzylating 4-bromo-5-mercapto-3-pyridazone (4.14g) with benzylchloride (2.53g.) in a similar way as described in the case Ⅳ, A-b. Anal. for this product (TABLE 4). Mixed M. p. by admixture with a sample prepared by the methad Ⅳ, A-a′ was 197°.

B. 4-*Chloro*-5-(2-*furfurylthio*)-3-*pyridazone* ($V_{i=b}$) —— The compound ($V_{i=b}$) (m. p. 133°, 4.5g. or 37.0% in yield) was obtained by furfurylthiolation of 4, 5-dichloro-3-pyridazone (8.25g.) with sodium 2-furfurylthiolate solution (2-furfurylmercaptan, 11.4g.) similarly as in the case of Ⅳ, A-a. Anal. for the product (TABLE 4).

C. 4-*Chloro*-5-(2-*thenylthio*)-3-*pyridazone* ($V_{i=c}$) —— a) The compound ($V_{i=c}$) (m. p 170°, 0.6g. or 23.3% in yield) was obtained by thenylthiolation of 4, 5-dichloro-3-pyridazone (1.65g.) with sodium 2-theylthiolate solution (2-thenylisothiuronium chloride (4.2g) in a mixture of 5% sodium hydroxide sol. (40ml.), concd. aq. ammonia (30ml.) and ethanol (40ml.), similarly as the case of Ⅳ, A-a. Mixed m. p. by admixture with a sample prepared by the method Ⅳ, C-b was 170°.

b) —— The compound ($V_{i=c}$) (m. p. 170°, 3.1g. or 60.0% in yield) was obtained by thenylation of 4-chloro-5-mercapto-3-pyridazone (3.25g.) with 2-thenyl chloride (5.30g.) in a similar manner as described on the method Ⅳ, A-b. Anal. for the product. (TABLE 4) Mixed m. p. by admixture with a sample prepared by the method Ⅳ, C-a was 170°.

Ⅴ. 4-*Mercapto*-5-*benzylthio*-3-*pyridazones* ($Ⅲ_i$)

A. 4-*Mercapto*-5-*benzylthio*-3-*pyridazone* ($Ⅲ_{i=a}$) —— a) 4-chloro-5-benzylthio-3-pyridazone ($V_{i=a}$) (0.5g.) was added to the sodium hydrosufide solution containing 32% aq. sodium hydrosulfiede sol. (0.7g.) in ethanol (30ml.) and the mixture was heated under reflux for 5 hr. Excess of ethanol was removed in a vacuum, residual solid was treated with water and filtered. Filtrate was acidified with concd. hydrochloric acid to pH=ca. 1. Precipitated solid was collected by filtration, washed with water and recrystallized from ethanol to give 4-*mercapto*-5-*benzylthio*-3-*pyridazone* ($Ⅲ_{i=a}$) (m. p. 186°, 0.35g. or 75.0% in yield) in greenish yellow crystals. Mixed m. p. by admixture with a sample (m. p. 186°) ($Ⅲ_a$) formed as a by-product in the reaction 2 was 186°.

Anal. Calcd. for $C_{11}H_{10}ON_2S_2$ (250.338) : C, 52.77; H, 4.03; N, 11.19. Found : C, 52.90; H, 3.93; N, 11.08.

b) 4-Bromo-5-benzylthio-3-pyridazone ($V_{i=a'}$) (1.49g) was allowed to react with sodium hydrosulfide solution in a similar manner as described on the method V, A-a, to produce the compound $III_{i=a}$ (1.10g or 88.0% in yield), m.p. 186° undepressed on admixture with an authentic specimen, in geenish yellow crystals.

B. 4-*Mercapto*-5-(2-*furfurylthio*)-3-*pyridazone* ($III_{i=b}$)

4-Chloro-5-(2-furfurylthio)-3-pyridazone ($V_{i=b}$) (1.10g) was allowed to react with sodium hydrosulfide solution (32% NaSH sol. (1.70g) in ethanol (75ml)) similarly as in the case of the V, A-a, to form 4-*mercapto*-5(2-*furfurylthio*)-3-*pyridazone* ($III_{i=b}$) (0.75g or 68.8% in yield), m.p. 145° undepressed on admixture with a sample (III_b) formed as a by-product in the reaction 2, in greenish yellow crystals.

C. 4-*Mercapto*-5-(2-*thenylthio*)-3-*pyridazone* ($III_{i=c}$)

By treating 4-*chloro*-5-(2-*thenylthio*)-3-*pyridazone* ($V_{i=c}$) (1.29g) with sodium hydrosulfide solution (32% NaSH sol. (11.70g) in ethanol (75ml)), similarly as described on the method V, A-a, 4-*mercapto*-5-(2-*thenylthio*)-3-*pyridazone* ($III_{i=c}$) (0.9g or 73.2% in yield), m.p. 153° undepressed on admixture with a sample (III_c) formed as a by-product in the reaction 2, in greenish yellow crystals, was obtained.

VI. 4,5-*Bis*(*benzylthio*)-3-*pyridazones by other miscellaneous preparations.*

A. 4,5-*Bis*(*benzylthio*)-3-*pyridazone* —— a) 4-*Chloro*-5-*benzylthio*-3-*pyridazone* ($V_{i=a}$) (0.51g) was added to sodium benzylthiolate solution containing benzylmercaptan (0.30g) in a mixture of 5% sodium hydroxide solution (4ml) and ethanol (4ml), and the whole was heated under reflux for 3 hours.

Reaction mixture was acidified with concd. hydrochloric acid, precipitated product was collected, washed with water, dried and recrystallized from ethanol. 4,5-*Bis*(*benzylthio*)-3-*pyridazone* (0.47g or 69.1% in yield), m.p. 160°C undepressed on admixture with a sample prepared by the method V A-c, was obtained.

b) 4,5-*Bis*(*benzylthio*)-3-*pyridazone* (0.60g or 88.2% in yield), m.p. 160°, was obtained by treating 4-*bromo*-5-*benzylthio*-3-*pyridazone* ($V_{i=a'}$) (0.59g) with sodium benzylthiolate, in a similar manner as described on the Method V, A-a.

c) 4-*Mercapto*-5-*benzylthio*-3-*pyridazone* (III_a) (0.50g) was dissolved in a mixture of 5% sodium hydroxide solution (4ml) and ethanol (7ml) and to the solution was added benzylchloride (0.28g) with stirring.

The mixture was kept stirred at room temperature for 5 hours, and colorless crystals separated meanwhile increasad gradually. Reaction mixture was acidified with concd. hydrochloric acid and precipitated solid were collected, washed with water, dried, and recrystallized from ethanol. 4,5-*Bis*(*benzylthio*)-3-*pyridazone*, m.p. 160° undepressed on admixture with a sample prepared by the method VI, A-a, 0.55g or 80% in yield, was obtained.

Calcd. for $C_{18}H_{16}ON_2S_2$ (340.456) : C, 63.32; H, 4.74; N, 8.23. Found: C, 63.63; H, 4.73; N, 8.59.

d) A mixture of 4-*chloro*-5-*mercapto*-3-*pyridazone* (IV) (0.81g), 32% aq. sodium hydrosulfide (1.70g) and ethanol (75ml) were placed in a closed glass tube and heated in a boiling water bath for 10 hours. Reaction mixture was concentrated in a vacuum to dryness, residual solid was dissolved in water and filtered. Alkaline filtrate was acidified with concd. hydrochloric acid to precipitate crude 4,5-*dimercapto*-3-*pyridazone*

(VI) (m. p. >300°, pale yellow crystals, 0.58g). Starting from 4-bromo-5-mercapto-3-pyridazone (IV′) (1.04g) and similarly treating as above, the same product (VI) (0.57g) was obtained.

Crude 4,5-dimercapto-3-pyridazone (0.68g) was dissolved in 5% sodium hydroxide solution (16ml) and to the solution was added benzylchloride (1.26g) in ethanol (16ml) with stirring. The mixture was stirred at room temperature for 3 hours, and then acidified with concd. hydrochloric acid. Precipitated product was collected, washed with water, dried, and recrystallized from ethanol to give 4,5-*bis*(*benzylthio*)-3-*pyridazone* (0.85g or 60.0% in yield), m. p. 160° showed no depression on admixture with a authentic specimen.

Anal. Calcd. for $C_{18}H_{16}ON_2S_2$ (340.456) : C, 63.32; H, 4.74; N, 8.23. Found : C, 63.44; H, 4.83; N, 8.35.

B. 4,5-*Bis*(2-*thenylthio*)-3-*pyridazone* (IIc) —— a) 4-Chloro-5-(2-thenylthio)-3-pyridazone (Vi=c) (0.52g) was heated with sodium 2-thenylthiolate solution containing 2-thenylisothiuronium chloride (0.84g) in a mixture of 5% sodium hydroxide solution (8ml) and ethanol (8ml), under reflux for 3 hours.

Reaction mixture was acidified with glacial acetic acid, precipitated solid was collected, washed with water, dried, and recrystallized from ethanol. 4,5-*Bis* (2-*thenylthio*)-3-*pyridazone* (0.45g or 63.7% in yield) melted at 121° undepressed on admixture with an authentic specimen prepared by the method on the reaction 1, was obtained.

b) 2-Thenylchloride (0.30g) was added to the sodium thiolate solution contaiding 4-*mercapto*-5-(2-*thenylthio*)-3-*pyridazone* (IIIi=c) (0.30g) in a mixture of 5% sodium hydroxide solution (4ml) and ethanol (4ml) and the whole was allowed to stand, with occasionally shaking, at room temperature for 1 hour.

Almost similarly treating the reactiod mixture as described above, 4,5-bis(2-thenylthio)-3-pyridazone (0.15g or 35.4% in yield) melting at 121° undepressed on admixture with an authentic specimen, was obtained.

VII. 4-(4-*Morpholino*)-3-*pyridazone* (VIII) and 5-(4-*morpholino*)-3-*pyridazone* (XI)

A. 4-(4-*Morpholino*)-5-*benzylthio*-3-*pyridazone* (VII) —— 4-Bromo-5-benzylthio-3-pyridazone (Vi=a′) (0.63 g) and morpholine (4.35g) were heated together at 150 — 160° (bath temperature) for 4 hours. On cooling the reaction mixture, it was diluted with water (30ml) to precipitate colorless solid which was collected, washed with water, and recrystallized from ethanol. 4-(4-*morpholino*)-5-*benzylthio*-3-*pyridazone* (VII) (0.6g or 79.2% in yield) melted at 191° and shaped in pale yellow crystals.

Anal. Calcd. for $C_{15}H_{17}O_2N_3S$ (303.376) : C, 59.38; H, 5.65; N, 13.85 Found : C, 59.33; H, 5.78; N, 14.02.

The same compound, (VII) (m. p., 191°, 2.60g or 87.1% in yield) was also obtained, starting from 4-*chloro*-5-*benzylthio*-3-*pyridazone* (Vi=a) (2.53g), by the similar treatment as described above.

B. 4-(4-*Morpholino*)-3-*pyridazone* (VIII) —— 4-(4-Morpholino)-5-benzylthio-3-pyridazone (VII), (1.00g) was added to a mixture of Raney-nickel (4.0g), dimethylformamide (5ml) and water (1ml) and the whole was heated to 120 — 140° (bath temperature). Heating within the temperature range was continued for 16 hours. Reaction mixture was filtered while hot, residual solid was washed with hot ethanol several times and alcholic washings were combined to the filtrate. Combined solution was concentrated in a vacuum to dryness

and the residue was recrystallized from ethanol to give 4-(4-*morpholino*)-3-*pyridazone* (Ⅷ) (m. p., 176°, 0.22g or 36.8% in yield) in colorless crystals.

Anal. Calcd. for $C_8H_{11}O_2N_3$ (181.192) : C, 53.03; H, 6.12; N, 23.19. Found : C, 52.84; H, 6.18; N, 23.37.

C. 4-*Benzylthio*-5-(4-*morpholino*)-3-*pyridazone* (X) —— 4-Chloro-5-(4-morpholino)-3-pyridazone (Ⅸ)[11] (2.16g) and 32% aq. sodium hydrosulfide solution (7.00g) were placed in a closed glass tube and it was heated in a boiling water bath for 10 hours.

On cooling the reaction mixture, deposited solid was collected, dissolved in water (80ml) and filtered. Alkaline filtrate was acidified with concd. hydrochloric acid (2ml), precipitated product was collected, washed with water and recrystallized from ethanol. 4-*Mercapto*-5-(4-*morpholino*)-3-*pyridazone* (Ⅻ), m. p. 171°, yellowish green crystals, was obtained. Yield, 1.68g (78.8%).

Anal. Calcd. for $C_8H_{11}O_2N_3S$ (213.258) : C, 45.05; H, 5.19; N, 19.71. Found : C, 44.96; H, 5.27; N, 19.88.

I. R. cm^{-1}: ν_{S-H} 2505; $\nu_{C=O}$ 1630

The same compound (Ⅻ) (1.25g) was also prepared by treating 4-*bromo*-5-(4-*morpholino*)-3-*pyridazone* (Ⅸ′)[11] (2.60g) in a similar manner as described above.

Benzylchloride (0.76g) was added to the sodium thiolate solution containing 4-*mercapto*-5-(4-*morpholino*)-3-*pyridazone* (Ⅻ) (0.64g) in a mixture of 5% sodium hydroxide solution (4.8ml), 28% aq. ammonia (4.8ml) and ethanol (10ml) and the whole was allowed to stand at room temperature with occasionally skaking for 1.5 hours.

Reaction mixture was acidified with concd. hydrochloric acid to precipitate the product which was collected, washed with water, dried, and recrystallized from ethanol. 4-*Benzylthio*-5-(4-*morpholino*)-3-*pyridazone* (X)[11] (m. p. 201°, 0.7g or 77.0%) was obtained and this was identical in any respect with the compound (m. p. 201°) prepared by benzylthiolation[11] of 4-*bromo*-5-(4-*morpholino*)-3-*pyridazone* (Ⅸ′) in an anhydrous reaction condition (sodium amide in dry toluene) at rather elevated temperature.

Anal. Calcd. for $C_{15}H_{17}O_2N_3S$ (303.376) : C, 59.38; H, 5.65; N, 13.85. Found : C, 59.44; H, 5.89; N, 14.11.

I. R. cm^{-1} : $\nu_{C=O}$ 1630

D. 5-(4-*Morpholino*)-3-*pyridazone* (Ⅺ) —— a) A mixture of 4-*bromo*-5-(4-*morpholino*)-3-*pyridazone* (Ⅸ′) (1.30g), sodium hydroxide (0.40g) in water (70ml) and 5% palladium on charcoal (0.50g) was hydrogenated at a room temperature and atmospheric pressure. When theoretical amount of hydrogen was absorbed, the catalyst was removed by filtration from the reaction mixture, washed with water and the washings were cembined to the filtrate. Combined alkaline solution was neutralized with glacial acetic acid and concentrated in vacuo to dryness. Residual solid was collected, washed with a small amount of water and recrystallized from ethanol to give 5-(4-*morpholino*)-3-*pyridazone* (Ⅺ) (m. p. 260°, 0.40g) in colorless crystals. Mixed melting point on admixture with 4-(4-morpholino)-3-pyridazone (m. p. 176°) (Ⅷ) showed a marked depression, although no depression in melting point was observed in admixture of any pair of the derivatives, the compound derived from Ⅸ or Ⅸ′, the one from 3-chloro-4-(4-morpholino)-6-pyridazone (XIV) and the one from 4-(benzylthio)-5-(4-morpholino)-3-pyridazone (X).

Anal. Calcd. for $C_8H_{11}O_2N_3$ (181.192) : C, 53.03; H, 6.12; N, 23.19. Found : C, 52.77; H, 6.12; N, 23.20.

The same compound XI, (0.15g) was obtained by catalytic dechlorination of 4-*chloro*-5-(4-*morpholino*)-3-*pyridazone* (IX) (0.7g) in a similar manner.

b) By catalytic dechlorination of 3-*chloro*-4-(4-*morpholino*)-6-*pyridazone* (XIV) (0.40g), 5-(4-*morpholino*)-3-*pyridazone* (XI) (0.18g) was also obtained.

Anal. Calcd. for $C_8H_{11}O_2N_3$ (181.192) : C, 53.03; H, 6.12; N, 23.19. Found : C, 52.83; H, 6.07; N, 23.09.

c) 4-*Benzylthio*-5-(4-*morpholino*)-3-*pyridazone* (X)[11] (1.0g) was desulfurized by heating with Raney-nickel (3.0g) in a mixture of dimelthylformamide (5ml) and water (1ml), likewise as described on the VII-B, to produce 5-(4-*morpholino*)-3-*pyridazone* (XI), (0.1g), m. p., 260° undepressed on admixture with any sample prepared by the method VII-D-a or VII-D-b.

VIII. 4-(4-*Morpholino*)-*pyridazine* (XVI)

A. *Dechlorination of* 3-*chloro*-4-(4-*morpholino*)-*pyridazine* (XV) to 4-(4-*morpholino*)-*pyridazine* (XVI) *by catalytic hydrogenation* —— 4-(4-Morpholino)-3-pyridazone (VIII) (1.0g) in phosphorous oxychloride (5ml) was heated at 110-115° (bath temperature) for 3 hours. On cooling the reaction mixture, it was poured onto crushed ice, resulted mixture was neutralized with 10% sodium hydroxide solution, alkaline solution was extracted with chloroform and the extract was dried over anhydrous sodium sulfate. Dried chloroform solution was concentrated in a vacuum to dryness and residual solid was recrystallized from ethyl acetate. 3-*Chloro*-4-(4-*morpholino*)-*pyridazine* (XV), m. p. 123° (0.55g or 50.0% in yield), colorless crystals, was obtained.

Anal. Calcd. for $C_8H_{10}ON_3Cl$ (199.641) : N, 21.05; Found : N, 21.21.

To a solution of 3-*chloro*-4-(4-*morholino*)-*pyridazine* (XV) (0.37g) in a mixture of 5% sodium hydroxide solution (3ml) and ethanol (25ml), 5% palladium on charcoal (0.2g) was added and the mixture was hydrogenated at a room temperature and atmospheric pressure. When absorption of hydrogen stopped, the catalyst was removed by filtration from the reaction mixture, the filtrate was acidified with concd. hydrochloric acid, and acidic solution was concentrated in a vacuum. Concentrated solution was basified again with dilute sodium hydroxide solution, extracted with chloroform and the extract was dried over anhydrous sodium sulfate. Chloroform solution was concentrated in vacuo to dryness and the residue was recrystallized from ethyl acetate. 4-(4-*Morpholino*)-*pyridazine* (XVI) *hemi-hydrate*, m. p. 89° undepressed on admixture with any sample prepared from 3-chloro-5-(*m*orpholino)-pyridazine (XVII) or from 3,4-dichloro-5-(morpholino)-pyridazine (XVIII) by catalytic dechlorination, weighed 0.16g (37.9% in yield).

This compound formed a picrate (m. p. 191°).

Anal. Calcd. for $C_8H_{11}ON_3 \cdot \frac{1}{2}H_2O$ (174.202) : C, 55.15; H, 6.97; N, 24.12. Found : C, 54.70; H, 6.86; N, 24.39.

Anal. Calcd. for $C_{14}H_{14}O_8N_6$ (394.302) : C, 42.64; H, 3.58; N, 21.32. Found : C, 42.94; H, 3.58; N, 21.14.

B. *Dechlorination of* 3-*chloro*-5-(4-*morpholino*)-*pyridazine* (XVII) *to* 4-(4-*morpholino*)-*pyridazine* (XVI) *by catalytic hydrogenation.* —— 5-(4-*Morpholino*)-3-*pyridazone* (XI) (2.0g) was chloricnated,

similarly in the case of the compound Ⅷ, by heating with phosphorous oxychloride (10ml) to produce 3-*chloro*-5-(4-*morpholino*)-*pyridazine* (XⅦ), m. p. 114°, 1.0g (45.7% in yield) in colorless crystals.

Anal. Calcd. for $C_8H_{10}ON_3Cl$(199.641) : C, 48.13; H, 5.05; N, 21.05. Found : C, 48.44; H, 5.24; N, 20.90.

3-Chloro-5-(4-morpholino)-pyridazine (XⅦ) (0.85g) was dechlorinated in a similar manner as described on the compound XV, 4-(4-*morpholino*)-*pyridazine* (XⅥ) *hemi-hydrate* (m. p. 89°), 0.40g was obtained. Either this compound or its picrate (m. p., 191°) was identical with the corresponding sample prepared from the compound XV, respectively.

Anal. Calcd. for $C_8H_{11}ON_8\frac{1}{2}H_2O$ (174.202) : C, 55.15; H, 6.97; N, 24.12. Found : C, 54.84; H, 6.83; N, 24.02.

Anal. Calcd. for $C_{14}H_{14}O_8N_6$(394.302) : C, 42.64; H, 3.58; N, 21.32. Found : C, 42.85; H, 3.70; N, 21.47.

C. *Dechlorination of* 3,4-*dichloro*-5-(4-*morpholino*)-*pyridazine* (XⅧ) *to* 4-(4-*morpholino*)-*pyridazine* (XⅥ) *by catalytic hydrogenation.* —— 4-Chloro-5-(morpholino)-3-pyridazone (Ⅸ)[11] (8.0g) was chlorinated by heating with phosphorous oxychloride (40ml), in a similar manner as described on the method Ⅷ-A, 3,4-dichloro-5-(4-morpholino)-pyridazine (XⅧ), m. p. 107.5°, 4.02g, was obtained.

Anal. Calcd. for $C_8H_9ON_3Cl_2$(234.090) : C, 41.04; H, 3.88; N, 17.95. Found : C, 41.29; H, 4.14; N. 18.02.

3,4-*Dichloro*-5-(*Morpholino*)-*pyridazine* (XⅧ) (1.0g) was declorinated by catalylic hydrogenation, in a similar manner as described on the compound XV, 4-(4-*morpholino*)-*pyridazine* (XⅥ) *hemi-hydrate*, (0.3g) m. p. 89° undepressed on admixture with a sample prepared from the compound (XV), was produced and its picrate (m. p., 191°) was also idential with an authentic specimen.

Anal. Calcd. for $C_8H_{11}ON_3\frac{1}{2}H_2O$ (174.200) : C, 55.15; H, 6.97; N, 24.12. Found : C, 55.34; H, 6.72; N, 24.12.

Anal. Calcd. for $C_{14}H_{14}O_8N_6$ (394.302) : C, 42.64; H, 3.58; N, 21.32. Found : C, 42.84; H, 3.64; N, 21.22.

Ⅸ. *A reaction of* 4,5-*bis*(*benzylthio*)-3-*pyridazone with sodium benzylthiolate in the presence of sodium amide in dry toluene.*

4,5-Bis(benzylthio)-3-pyridazone (3.40g) was added to the sodium benzylthiolate suspension in toluene, prepared by heating benzylmercaptan (2.48g) with sodium amide (0.88g) in dry toluene (50ml) under reflux for 30 minutes, and the whole was heated under reflux for ca. 10 hours. Reaction mixture was concentrated in a vacuum to dryness, to the residual cake water (40ml) was added and the mixture was fully triturated. Residual solid was separated by filtration, washed with water (40ml) and washings were combined to the alkaline filtrate.

The residual solid was suspended in water (50ml) and acidified with concd. hydrochloric acid, recollected by filtration, washed with water, dried, and recystallized from ethanol. 4,5-*Bis*(*benzylthio*)-3-*pyridazone* (Ⅱa) (m. p., 160°C), 2.60g, was recovered. The alkaline filtrate was acidified with concd. hydrochloric acid to precipitate solid which was washed with water, dried, and recrystallized from ethanol. 4-*Mercapto*-5-*benzylthio*-3-*pyridazone* (Ⅲa) obtained weighed 0.10g (4.0% in yield) and melted at 186° undepressed on admixture with an authentic specimen.

Acknowledgment

This investigation was supported in part by Grant in Aid for Fundamental Scientific Research of the Ministry of Education and a grant from Tanabe Pharmaceutical Co., for which we express our appreciation.

The authors are grateful to Dr. J. Iwao for his interesting and helpful disscussion, to Dr. K. Abe and to Dr. T. Okuda for screening tests, and to Miss F. Uesugi and Miss T. Fujii for elemental analyses.

Thanks are also due to M. Yamazaki, T. Iwakuma and Y. Masaki for their assistances in the experimetal work.

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大野武男, 森逸男: クロルフルオレスセインの水銀反応について

Takeo Ohno, Itsuo Mori: Mercuration of Chlorofluoresceins

Mercuration of eight kinds of chlorofluorescein (2′-Cl, 4′-Cl, 2′,4′-Cl, 4′,5′-Cl, 2′,7′-Cl, 2′,5′-Cl, 2′,4′,5′-Cl, 2′,4′,7′-Cl-fl) was discussed and sterilizing effect of mercurichlorofluorescein was compared here.

フタレイン類の水銀化（以下 Hg 化と略記）反応に関しては古く White[1] が fluorescein（以下 fl. と略記），Bromofl.（以下 Brfl. と略記）の Hg 化反応を報告し，長瀬，大野[2] は mercurochrome の製造条件について詳しく検討した．またフタレイン類の化合物の Hg 化合物の殺菌効果については Candeli[3] が eosin と $Hg(OAc)_2$ の反応生成物について，Petrilli,[4] Rohatgi[5),6)] らが数種の Brfl. の Hg化合物について報告している．しかるに Clfl.