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78. Fumio Yoneda, Takayuki Ohtaka, and Yoshihiro Nitta :
Pyridazine Derivatives. VII.*¹ Syntheses of
1,2- and 2,3-Diazaphenothiazines.

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Due to the importance of phenothiazine and monoazaphenothiazine derivatives in medicinal chemistry it seemed of interest to investigate the diazaphenothiazines in which the two nitrogen atoms are adjacent in one of the benzenoid rings. There are three isomers *viz.* 10*H*-benzo[*b*]pyridazino[3,4-*e*][1,4]thiazine (A), 5*H*-benzo[*b*]pyridazino[4,3-*e*][1,4]thiazine (B), and 10*H*-benzo[*b*]pyridazino[4,5-*e*][1,4]thiazine (C) in this diazaphenothiazine. In the previous paper¹⁾ the preparation of the type (A) and (B) shown in

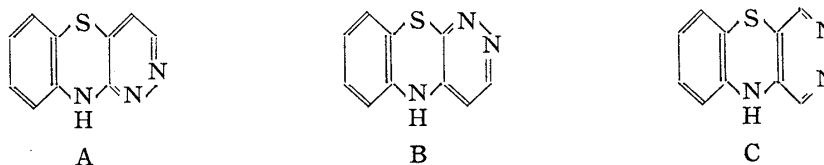


Chart 1.

Chart 1 was briefly described. This paper presents further information on the preparation of the type (A) and (C), and records some physical and chemical properties of this ring system.

3,4,5-Trichloropyridazine (I)²⁾ was used as a starting material for these compounds. It might be supposed that treatment of I with 2-aminothiophenol in methanolic potassium hydroxide solution would yield some of four types (D~G) in Chart 2.*³

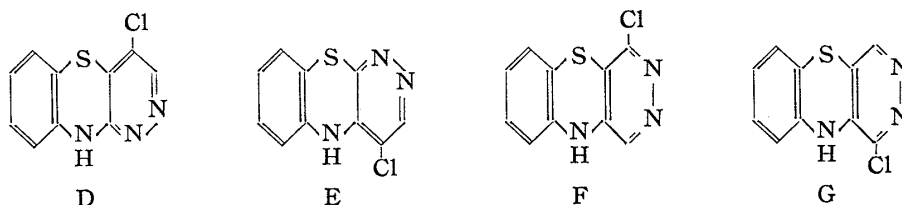


Chart 2.

*¹ Part VI : This Bulletin, 12, 1351 (1964).*² Takataminami-cho, Toshima-ku, Tokyo (米田文郎, 大高孝之, 新田義博).*³ Fig. 1 represents the π -electronic distributions of I calculated by a simple LCAO-MO method. The parameters used in calculation are shown in Fig. 2.

As can be seen from Fig. 1, there is no difference between the π -electron densities at the 3,4, and 5 positions and also between the superdelocalizabilities for nucleophilic reaction ($S_r^{(N)}$)³⁾ in these positions ($S_3^{(N)}=0.9806$, $S_4^{(N)}=0.9803$, $S_5^{(N)}=0.9804$). Consequently, it is thought that these three chlorines are active to the same extent, and it is difficult to estimate the product of reaction between

I and 2-aminothiophenol, in contrast to the clear estimation in the case of the reaction between 3,4,6-trichloropyridazine and 2-aminothiophenol, which will be reported in the following papers.

1) F. Yoneda, T. Ohtaka, Y. Nitta : This Bulletin, 11, 954 (1963).

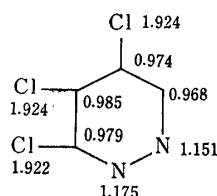
2) T. Kuraishi : *Ibid.*, 4, 497 (1956).3) K. Fukui, *et al.* : Bull. Chem. Soc. Japan, 27, 423 (1954).

Fig. 1.

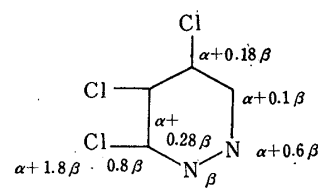


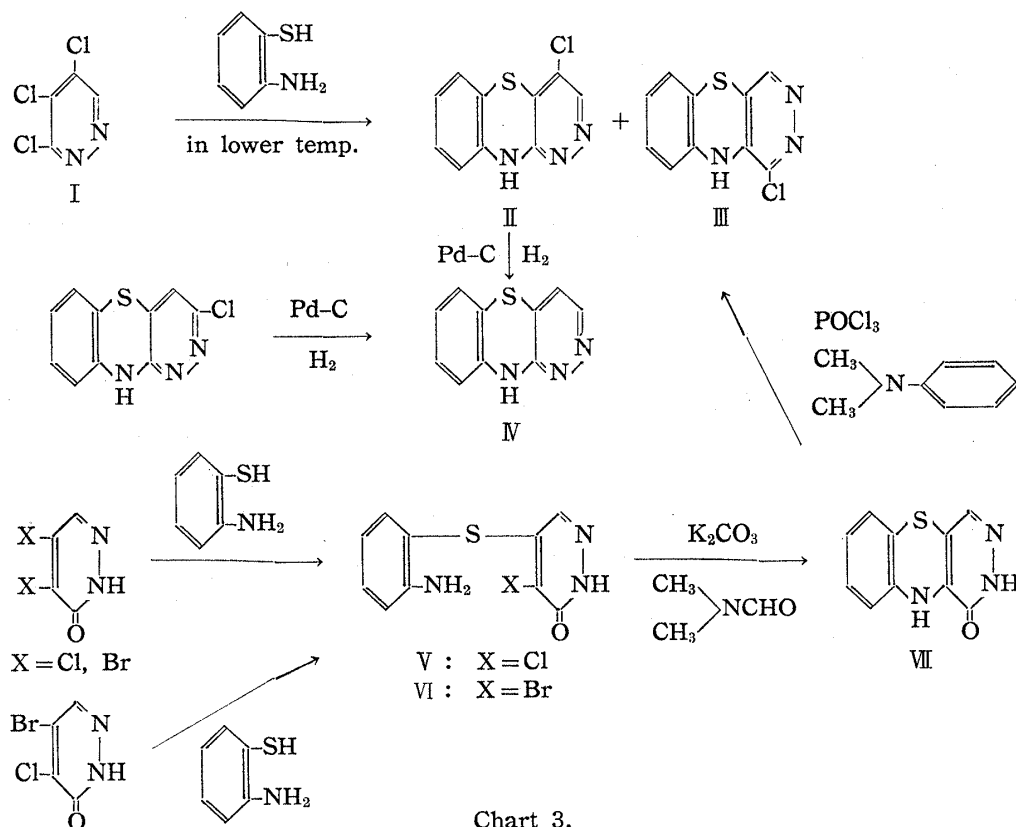
Fig. 2.

It is one of our aims to determine the structures of such reaction products.

Compound (I), when treated with 2-aminothiophenol in methanolic potassium hydroxide solution at temperature of 15~20°, produced a mixture of two compounds, the main product (II), m.p. 302°(decomp.), and the by-product (III), m.p. 267°(decomp.), which were separated by the different solubility in ethyl alcohol. A molecular formula of $C_{10}H_6N_3SCl$ was assigned to II or III, based on the elementary analysis and molecular weight measurement, hence it was thought that II and III belong to some of four types in Chart 2. Catalytic hydrogenation of II over palladium charcoal gave yellow needles (IV), m.p. 263°. IV proved to be identical with 10*H*-benzo[*b*]pyridazino[3,4-*e*][1,4]thiazine obtained from the known 3-chloro-10*H*-benzo[*b*]pyridazino[3,4-*e*][1,4]thiazine¹⁾ in a similar catalytic hydrogenation. Of four diazaphenothiazines in Chart 2, only D gives 10*H*-benzo[*b*]pyridazino[3,4-*e*][1,4]thiazine by catalytic dechlorination. The structure of compound (II) is therefore confirmed to be 4-chloro-10*H*-benzo[*b*]pyridazino[3,4-*e*][1,4]thiazine.

Since the ultraviolet spectrum of by-product (III) showed an absorption maximum at longer wavelength ($\lambda_{\max}$ max 268 $m\mu$) than A and B types, as stated below, and also its infrared spectrum differed from those of the latters, thus supposing that III belongs to C type, namely to either F or G in Chart 2.

Therefore, the following reactions were carried out in order to confirm the structure of III.



Treatment of 4,5-dichloro(or dibromo)-3(2*H*)-pyridazinone with 2-aminothiophenol in methanolic potassium hydroxide solution yielded 5-(2-aminophenylthio)-4-chloro (or bromo)-3(2*H*)pyridazinone (V and VI). V was obtained also by the condensation of 4-chloro-5-bromo-3(2*H*)-pyridazinone⁴⁾ with 2-aminothiophenol in the same way. V and VI were cyclized on heating with potassium carbonate in dimethylformamide to give

4) T. Kuraishi : This Bulletin, 6, 641 (1958).

10*H*-benzo[*b*]pyridazino[4,5-*e*][1,4]thiazine-1(2*H*)-one (VII) in good yields. Subsequent chlorination with phosphoryl chloride in *N,N*-dimethylaniline gave 1-chloro-10*H*-benzo[*b*]pyridazino[4,5-*e*][1,4]thiazine (III); the yield was very poor, however. This substance proved to be identical with the above-mentioned by-product (III) with respect to melting points and infrared spectra.

Reaction of I with 2-aminothiophenol in methanolic potassium hydroxide solution at 30~60° did not produce II and III, but gave the compound (VIII), m.p. above 290° (decomp.), whose analysis led to a formula of C₁₀H₁₂N₄S₂. VIII was supported to be 4-(2-aminophenylthio)-10*H*-benzo[*b*]pyridazino[3,4-*e*][1,4]thiazine, on the basis of the fact that VIII was positive in the diazo reaction of the primary amine and its ultraviolet spectra showed an absorption maximum at the same position ($\lambda_{\max}$ 248 m μ) as II. In this reaction, treatment of 1 mole of I with 2 mole of 2-aminothiophenol led to VIII in better yield. II was not converted into VIII by treatment with 2-aminothiophenol in methanolic potassium hydroxide solution owing to considerable inactivity of chlorine of II. Therefore it seemed likely that II was converted into VIII through an intermediate, 4,5-bis(2-aminophenylthio)-3-chloropyridazine.

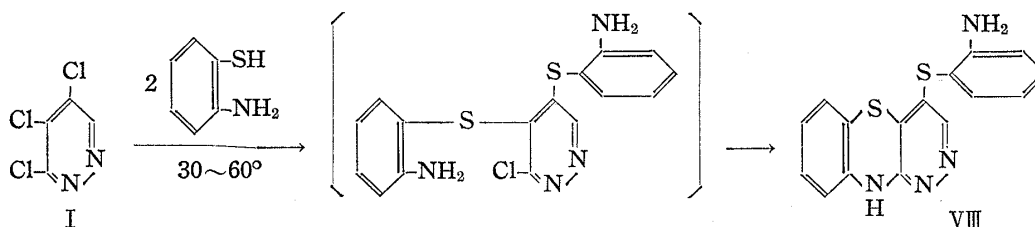


Chart 4.

I on treatment with 2-methylaminothiophenol in methanolic potassium hydroxide solution at lower temperature yielded only 1-chloro-10-methyl-10*H*-benzo[*b*]pyridazino[4,5-*e*][1,4]thiazine (IX), but no isomer, 4-chloro-10-methyl-10*H*-benzo[*b*]pyridazino[3,4-*e*][1,4]thiazine was obtained. In this case, proof of the structure of IX was obtained from the fact that the ultraviolet spectra of IX was very much like III. 4-(2-Methylamino-phenylthio)-10*H*-benzo[*b*]pyridazino[3,4-*e*][1,4]thiazine (X) was also synthesized from I and 2-methylaminothiophenol using the same method as that for preparing VIII.

Next, 4-methoxy- (XI) and 4-ethoxy-10*H*-benzo[*b*]pyridazino[3,4-*e*][1,4]thiazine (XII) were prepared by heating I under pressure with sodium methoxide and ethoxide in the corresponding alcohol, respectively. 4-Dimethylamino-10*H*-benzo[*b*]pyridazino[3,4-*e*][1,4]thiazine (XIII) was obtained by heating the compound (I) under pressure with dimethylamine in ethyl alcohol. In a similar way compound (III) was converted to ethoxy-10*H*-benzo[*b*]pyridazino[4,5-*e*][1,4]thiazine (XIV) by reaction with sodium ethoxide.

The ultraviolet absorption spectra of 1,2-(type A), 3,4-(type B), and 2,3-diazaphenothiazines (type C) obtained in the present and previous papers are shown in Figs. 1, and 2. As can be seen from these figures, A, B, and C types showed their different absorptions in ultraviolet spectra and in general the absorption maxima were shifted to longer wave lengths in increasing order of A, B, and C types. The spectra of the 3-substituted derivatives in A type were very similar to those of the 4-substituted derivatives. The A type was distinguished by an intense peak at 240~250 m μ accompanied with a shoulder at 270~280 m μ . B and C types have maxima at 250 m μ region and 270 m μ region, respectively, without shoulders. The *N*-methyl derivatives showed also the same absorptions as *N*-free derivatives. The above-mentioned behaviour in ultraviolet absorption would be of use to estimate the structure of newly synthesized diazaphenothiazines.

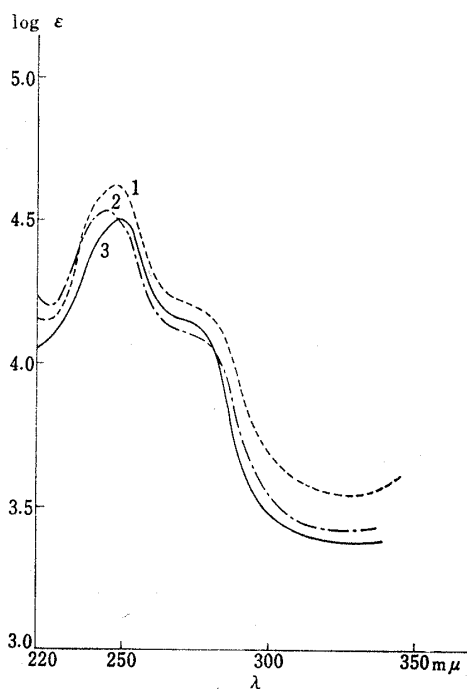


Fig. 1.

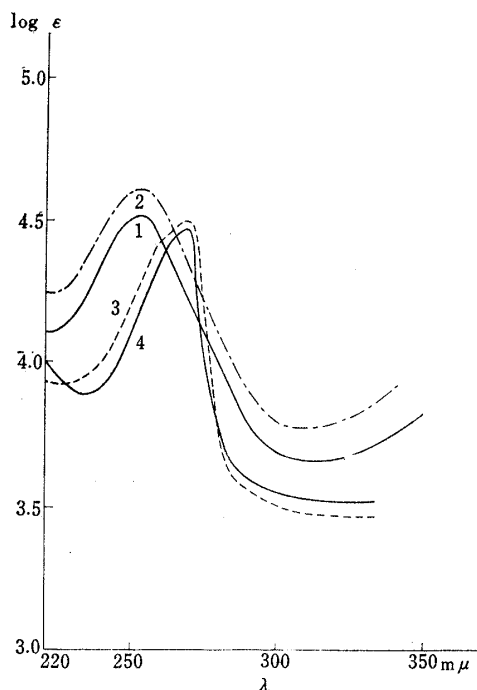
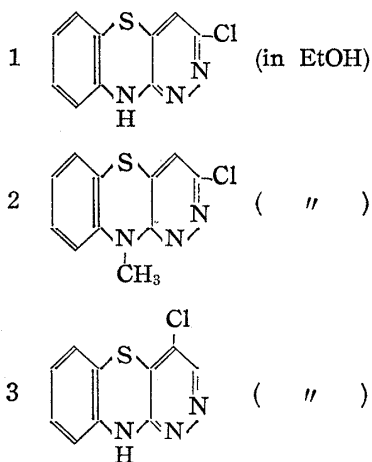
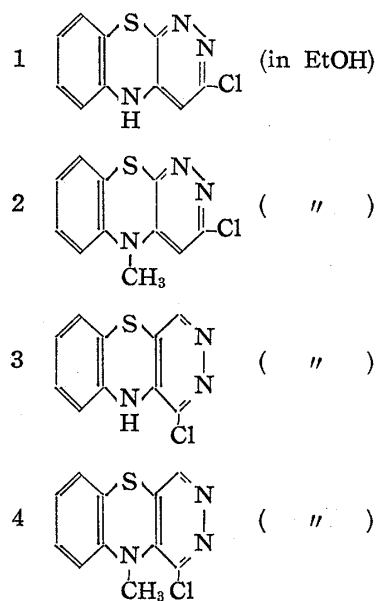
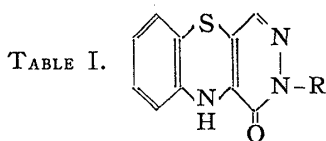


Fig. 2.



10*H*-benzo[*b*]pyridazino[4,5-*e*][1,4]thiazin-1(2*H*)-one (VII), having a substitutive hydrogen at the 2-position, was converted into the 2-substituted derivatives in expectation of pharmacological effects: VII was treated with methyl iodide, *N,N*-dimethyl-2-chloroethylamine, *N,N*-diethyl-2-chloroethylamine, 1-(2-chloroethyl)pyrrolidine, 1-(2-chloroethyl)piperidine, and 1-(2-chloroethyl)morpholine in the presence of sodium alkoxide to yield 2-methyl- (XV), 2-(2-dimethylaminoethyl)- (XVI), 2-(2-diethylaminoethyl)- (XVII), 2-[2-(1-pyrrolidinyl)ethyl]- (XVIII), 2-(2-piperidinoethyl)- (XIX), and 2-(2-morpholinoethyl)-10*H*-benzo[*b*]pyridazino[4,5-*e*][1,4]thiazin-1(2*H*)-one (XX) (Table I), respectively.



No.	R	m.p. (°C)	Formula	Analysis (%)					
				Calcd.			Found		
				C	H	N	C	H	N
XV	CH ₃ -	>300	C ₁₁ H ₉ ON ₃ S	57.14	3.92	18.18	57.47	3.98	17.82
XVI	$\begin{array}{c} \text{CH}_3 \\ \text{CH}_3 \end{array} \text{N-CH}_2\text{CH}_2\text{-}$	248	C ₁₄ H ₁₆ ON ₄ S	58.32	5.59	19.44	58.55	5.58	19.69
XVII	$\begin{array}{c} \text{C}_2\text{H}_5 \\ \text{C}_2\text{H}_5 \end{array} \text{N-CH}_2\text{CH}_2\text{-}$	257	C ₁₆ H ₂₀ ON ₄ S	60.74	6.37	17.71	61.02	6.41	17.92
XVIII	 N-CH ₂ CH ₂ -	259	C ₁₆ H ₁₈ ON ₄ S	61.13	5.77	17.83	61.18	5.98	17.92
XIX	 N-CH ₂ CH ₂ -	263	C ₁₇ H ₂₀ ON ₄ S	62.18	6.14	17.06	62.29	6.25	16.93
XX	 N-CH ₂ CH ₂ -	272	C ₁₆ H ₁₈ O ₂ N ₄ S	58.17	5.49	16.96	58.02	5.68	16.82

Experimental^{*4}

4-Chloro-10H-benzo[*b*]pyridazino[3,4-*e*][1,4]thiazine (II) and 1-Chloro-10H-benzo[*b*]pyridazino[4,5-*e*][1,4]thiazine (III)—To a stirred solution of 3,4,5-trichloropyridazine (2.0 g.) in 30 ml. of EtOH was added slowly a solution of 2-aminothiophenol (1.25 g.) and KOH (0.7 g.) in 30 ml. of EtOH at 15 to 20° with cooling (ice-water bath), and after 1 hr. a heavy precipitate separated. The crude product was washed with H₂O, and dried. Recrystallization from EtOH yielded 1.2 g. of yellow prisms (II), m.p. 300~302° (decomp.) *Anal.* Calcd. for C₁₀H₆N₃ClS: C, 50.97; H, 2.57; N, 17.83. Found: C, 51.02; H, 2.87; N, 17.91.

The mother liquors of II were concentrated to dryness and the residue (0.4 g.) was crystallized from toluene to give yellow needles (III), m.p. 263° (decomp.). *Anal.* Calcd. for C₁₀H₆N₃ClS: C, 50.97; H, 2.57; N, 17.83. Found: C, 51.02; H, 2.87; N, 17.91.

10H-Benzo[*b*]pyridazino[3,4-*e*][1,4]thiazine (IV)—A solution of II (5.0 g.) in 500 ml. of EtOH was hydrogenated over Pd-C (10%, 0.3 g.) until 480 ml. of H₂ was consumed and filtered. The catalyst on carbon was washed with EtOH (100 ml.). The combined filtrate and washings were concentrated to dryness. The residue was crystallized from EtOH to yield 3.5 g. of yellow needles, m.p. 261~263°. *Anal.* Calcd. for C₁₀H₇N₃S: C, 59.70; H, 3.59; N, 20.89. Found: C, 59.94; H, 3.47; N, 21.18.

5-(2-Aminophenylthio)-4-chloro-3(2H)-pyridazinone (V)—To a solution of 2-aminothiophenol (1.25 g.) and NaOH (0.7 g.) in 50 ml. of MeOH was added 4,5-dichloro-3(2H)-pyridazinone (1.65 g.) with stirring for 2 hr. in room temperature. The separated crystals were filtered off and washed with H₂O. After recrystallization from MeOH+H₂O, pale yellow needles (2.4 g.), m.p. 198° (decomp.) was obtained. *Anal.* Calcd. for C₁₀H₈ON₃ClS: C, 47.34; H, 3.18; N, 16.56. Found: C, 46.84; H, 3.52; N, 16.58.

5-(2-Aminophenylthio)-4-bromo-3(2H)-pyridazinone (VI)—4,5-Dibromo-3(2H)-pyridazinone (2.54 g.) were added to a solution of 2-aminothiophenol (1.25 g.) and NaOH (0.7 g.) in 50 ml. of MeOH and treated as described for V. Pale yellow needles (2.6 g.), m.p. 260~261° (decomp.). *Anal.* Calcd. for C₁₀H₈ON₃BrS·½H₂O: C, 39.10; H, 2.98; N, 13.68. Found: C, 38.64; H, 3.10; N, 13.53.

10H-Benzo[*b*]pyridazino[4,5-*e*][1,4]thiazin-1(2H)-one (VII)—V or VI (3.0 g.) was heated with 3.0 g. of K₂CO₃ in 50 ml. of dimethylformide under reflux for 8 hr. Filtration of K₂CO₃ followed by evaporation of the filtrate to dryness afforded 2.0 g. of VII. Washing of the product with H₂O, followed by recrystallization from EtOH+H₂O afforded orange crystals (1.5 g.), m.p. >300°. *Anal.* Calcd. for C₁₀H₇ON₃S·H₂O: C, 51.05; H, 3.86; N, 17.86. Found: C, 51.18; H, 3.86; N, 18.26.

Chlorination of VII—A suspension of VII (1.5 g.) in POCl₃ (20 ml.) and N,N-dimethylaniline (5 ml.) was refluxed until VII was completely dissolved. This required 3 hr. Excess POCl₃ was removed *in vacuo*. The residue was poured into ice-water and the precipitate was collected. After recrystallization from toluene, III (0.4 g.), d.p. 267°, was obtained in yellow needles. *Anal.* Calcd. for C₁₀H₆N₃ClS: C, 50.97; H, 2.57; N, 17.83. Found: C, 51.19; H, 2.63; N, 17.08.

This sample had the same IR spectra as those of authentic sample of III.

^{*4} All melting points were uncorrected.

4-(2-Aminophenylthio)-10H-benzo[*b*]pyridazino[3,4-*e*][1,4]thiazine (VIII)—I (1.83 g.) was added to a solution of 2-aminothiophenol (2.5 g.) and KOH (1.4 g.) in 50 ml. of MeOH and stirred for 1 hr. at ca. 40°. The precipitate was crystallized from EtOH to yield yellow needles, m.p. above 290°. *Anal.* Calcd. for C₁₆H₁₂N₄S₂: C, 59.23; H, 3.73; N, 17.27; S, 19.77. Found: C, 59.43; H, 3.85; N, 17.45; S, 18.57.

1-Chloro-10-methyl-10H-benzo[*b*]pyridazino[4,5-*e*][1,4]thiazine (IX)—3-Methyl-2(3*H*)-benzothiazolinone (4.4 g.) were heated in 100 ml. EtOH containing KOH (17.6 g.) under reflux for 3 to 4 hr. To the solution was added slowly a solution of 5.32 g. of I in 100 ml. EtOH with stirring and cooling (ice-water bath). The precipitate was filtered off and the filtrate was concentrated to dryness. The residue was recrystallized from EtOH to give 1 g. of yellow needles, melting 175°. *Anal.* Calcd. for C₁₁H₈N₃ClS: C, 52.91; H, 3.21; N, 16.83. Found: C, 52.98; H, 3.40; N, 17.18.

4-(2-Methylaminophenylthio)-10H-benzo[*b*]pyridazino[3,4-*e*][1,4]thiazine (X)—3-Methyl-2(3*H*)-benzothiazolinone (2.2 g.) were refluxed in a solution of KOH (8.8 g.) in 50 ml. MeOH for 3 hr. To the solution was added a solution of I (2.7 g.) of in 20 ml. MeOH with stirring in room temperature. After standing overnight, crystals were separated. The crude product crystallized from (CH₃)₂CO to yield colourless needles (3.5 g.), m.p. 172°. *Anal.* Calcd. for C₁₈H₁₆N₄S₂: C, 61.36; H, 4.58; N, 15.90. Found: C, 61.86; H, 4.52; N, 15.85.

4-Methoxy-10H-benzo[*b*]pyridazino[3,4-*e*][1,4]thiazine (XI)—II (1.2 g.) was heated in 50 ml. MeOH containing 0.15 g. of Na in a sealed tube for 5 hr. at 160°. After removal of NaCl, the filtrate was concentrated and diluted with H₂O. The precipitated product was collected, washed with H₂O, and dried. Recrystallization from EtOH gave yellow needles (0.8 g.), d.p. 244~246°. *Anal.* Calcd. for C₁₁H₉ON₃S: C, 57.14; H, 3.92; N, 18.18. Found: C, 57.07; H, 3.81; N, 17.96.

4-Ethoxy-10H-benzo[*b*]pyridazino[3,4-*e*][1,4]thiazine (XII)—II (1.2 g.) was added to 50 ml. EtOH containing 0.15 g. of Na and treated as described for XI to give yellow needles (0.8 g.), d.p. 240°. *Anal.* Calcd. for C₁₂H₁₁N₃OS: C, 58.77; H, 4.52; N, 17.14. Found: C, 58.95; H, 4.35; N, 16.84.

4-Dimethylamino-10H-benzo[*b*]pyridazino[3,4-*e*][1,4]thiazine (XIII)—II (0.25 g.) was heated in 400 ml. EtOH containing excess dimethylamine in a sealed tube for 3 hr. at 160°. After evaporation of solvent, the residue was diluted with H₂O. The separated solid was filtered off and recrystallized from EtOH to yield 0.2 g. of yellow needles, melting 231°(decomp.). *Anal.* Calcd. for C₁₂H₁₂N₄S: C, 59.01; H, 4.95; N, 22.94. Found: C, 59.41; H, 5.15; N, 23.04.

1-Ethoxy-10H-benzo[*b*]pyridazino[4,5-*e*][1,4]thiazine (XIV)—III (1.2 g.) was added to 50 ml. EtOH containing 0.15 g. of Na and treated as described for XI to give yellow needles (0.8 g.), m.p. 238°(decomp.). *Anal.* Calcd. for C₁₂H₁₁N₃OS: C, 58.77; H, 4.52. Found: C, 58.82; H, 4.49.

2-(2-Dimethylaminoethyl)-10H-benzo[*b*]pyridazino[4,5-*e*][1,4]thiazin-1(2*H*)-one (XVI)—IV (2.4 g.) were dissolved in a solution of Na (0.75 g.) in 100 ml. EtOH, added with 1.5 g. of N,N-dimethyl-2-chloroethylamine hydrochloride, and refluxed for 4 hr. After evaporation of EtOH and washing with H₂O, the separated crystals were recrystallized from EtOH to give 2.5 g. of XVI in orange needles (Table I).

We thank Dr. T. Akiba, Director of this laboratory, for his encouragement, and also to the members of analysis room of this laboratory for elemental analyses.

Summary

3,4,5-Trichloropyridazine on treatment with 2-aminothiophenol gave 4-chloro-10H-benzo[*b*]pyridazino[3,4-*e*][1,4]thiazine (II) and 1-chloro-10H-benzo[*b*]pyridazino[4,5-*e*][1,4]thiazine (III). II was converted into 10H-benzo[*b*]pyridazino[3,4-*e*][1,4]thiazine by catalytic dechlorination. Treatment of 4,5-dichloro-3(2*H*)-pyridazinone with 2-aminothiophenol afforded 5-(2-aminophenylthio)-4-chloro-3(2*H*)-pyridazinone, which was cyclized on heating with potassium carbonate in dimethylformamide to yield 10H-benzo[*b*]pyridazino[4,5-*e*][1,4]thiazin-1(2*H*)-one. Chlorination of the latter with phosphoryl chloride and N,N-dimethylaniline afforded III. Several 2-substituted-10H-benzo[*b*]pyridazino[4,5-*e*][1,4]thiazin-1(2*H*)-ones were synthesized.

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