Chem. Pharm. Bull. 13(5) 580~585 (1965)

UDC 547.852.9.07

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

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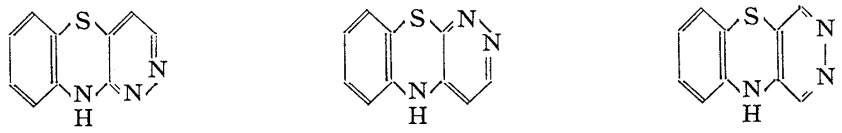
Due to the importance of phenothiazine and monoazaphenothiazine derivatives in medicinal chemistry it seemed of interest to investigate the diazaphenothiazines in which the two nitrogen atoms are adjacent in one of the benzenoid rings. There are three isomers *viz.* 10*H*-benzo[*b*]pyridazino[3,4-*e*][1,4]thiazine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

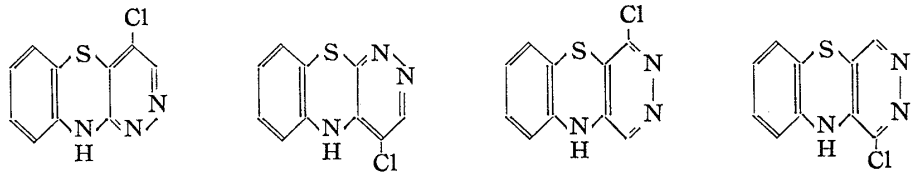


A B C

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



D E F G

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.

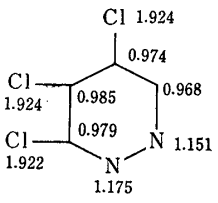


Fig. 1.

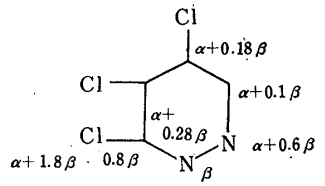


Fig. 2.

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 ($Sr^{(N)}$)[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).

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]thiazine[1] 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 (λ_{max} max 268 mμ) 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.

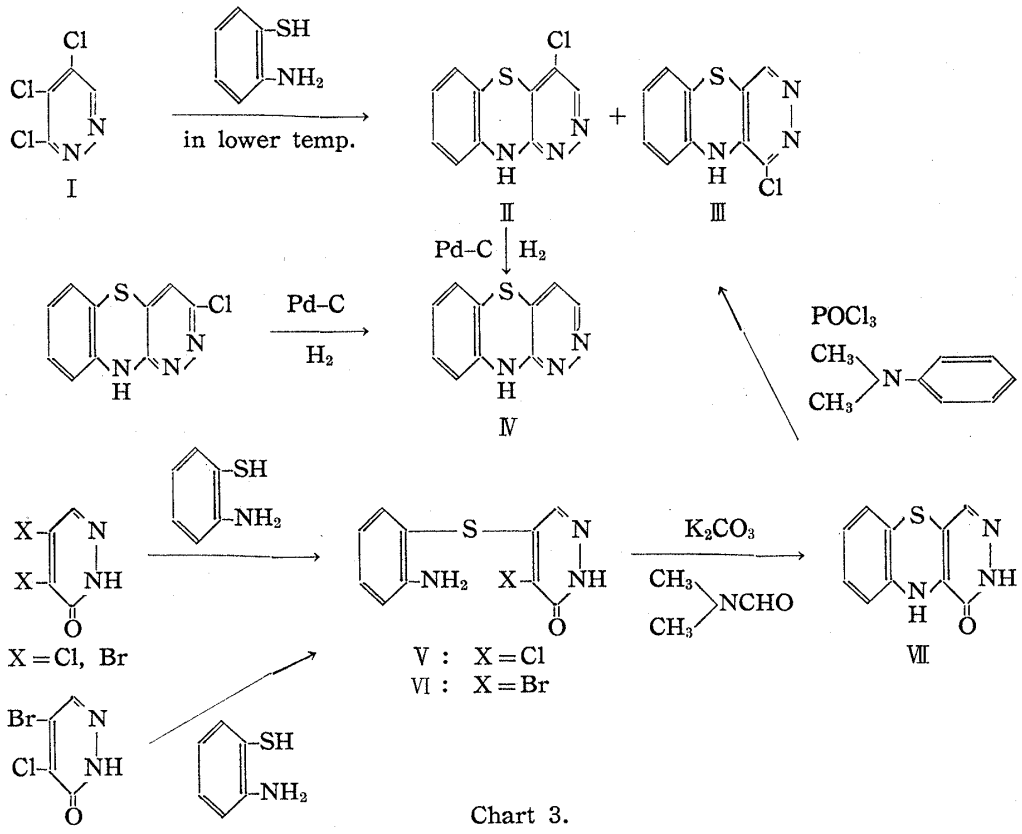


Chart 3.

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*)-pyridazinone[4] 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 $C_{10}H_{12}N_4S_2$. 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 (λ_{max} 248 mμ) 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.

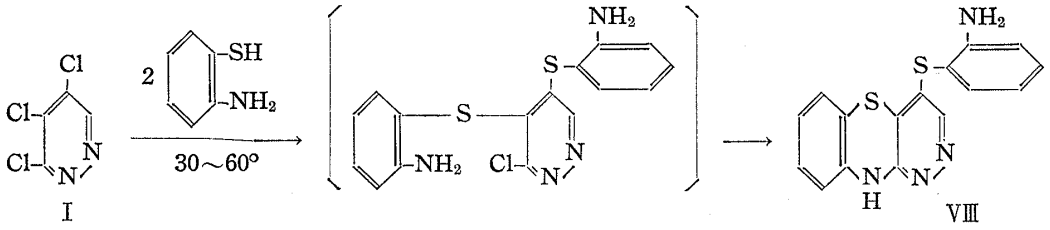


Chart 4.

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*]pyridazine[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 mμ accompanied with a shoulder at 270~280 mμ. B and C types have maxima at 250 mμ region and 270 mμ region, respectively, without shoulders. The N-methyl derivatives showed also the same absorptons as N-free derivatives. The above-mentioned behaviour in ultraviolet absorption would be of use to estimate the structure of newly synthesized diazaphenothiazines.

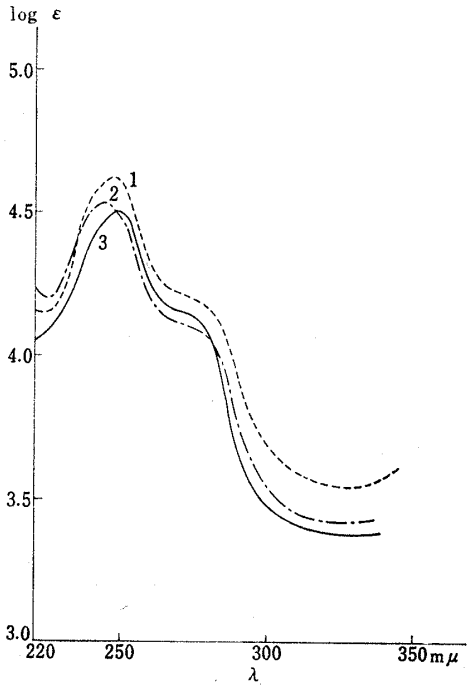


Fig. 1.

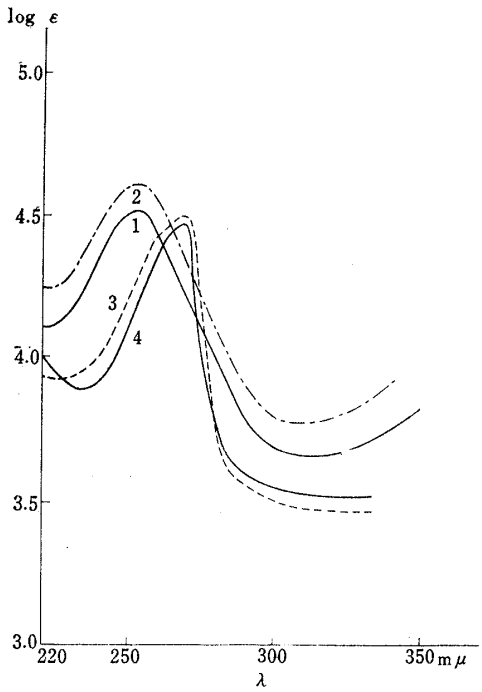
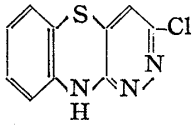
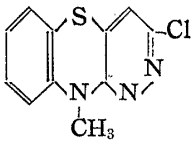
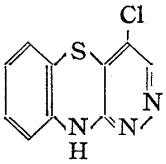
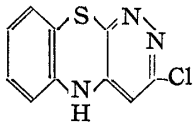


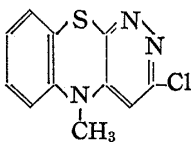
Fig. 2.

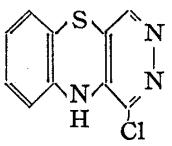
1  (in EtOH)

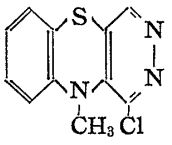
2  (〃)

3  (〃)

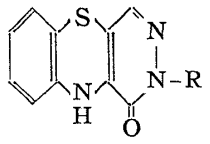
1  (in EtOH)

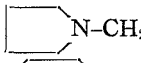
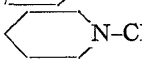
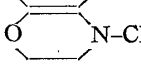
2  (〃)

3  (〃)

4  (〃)

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 methyliodide, 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.

Table I. 

No.	R	m.p. (°C)	Formula	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
XV	CH_3–	>300	$C_{11}H_9ON_3S$	57.14	3.92	18.18	57.47	3.98	17.82
XVI	$(CH_3)_2N$–CH_2CH_2–	248	$C_{14}H_{16}ON_4S$	58.32	5.59	19.44	58.55	5.58	19.69
XVII	$(C_2H_5)_2N$–CH_2CH_2–	257	$C_{16}H_{20}ON_4S$	60.74	6.37	17.71	61.02	6.41	17.92
XVIII		259	$C_{16}H_{18}ON_4S$	61.13	5.77	17.83	61.18	5.98	17.92
XIX		263	$C_{17}H_{20}ON_4S$	62.18	6.14	17.06	62.29	6.25	16.93
XX		272	$C_{16}H_{18}O_2N_4S$	58.17	5.49	16.96	58.02	5.68	16.82

Experimental*4

4-Chloro-10*H*-benzo[*b*]pyridazino[3,4-*e*][1,4]thiazine (II) and 1-Chloro-10*H*-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 H_2O, and dried. Recrystallization from EtOH yielded 1.2 g. of yellow prisms (II), m.p. 300~302° (decomp.) *Anal.* Calcd. for $C_{10}H_6N_3ClS$: 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 $C_{10}H_6N_3ClS$: C, 50.97; H, 2.57; N, 17.83. Found: C, 51.02; H, 2.87; N, 17.91.

10*H*-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 H_2 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 $C_{10}H_7N_3S$: 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(2*H*)-pyridazinone (V)——To a solution of 2-amionthiophenol (1.25 g.) and NaOH (0.7 g.) in 50 ml. of MeOH was added 4,5-dichloro-3(2*H*)-pyridazinone (1.65 g.) with stirring for 2 hr. in room temperature. The separated crystalls were filtered off and washed with H_2O. After recrystallization from MeOH+H_2O, pale yellow needles (2.4 g.), m.p. 198° (decomp.) was obtained. *Anal.* Calcd. for $C_{10}H_8ON_3ClS$: 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(2*H*)-pyridazinone (VI)——4,5-Dibromo-3(2*H*)-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 $C_{10}H_8ON_3BrS \cdot \frac{1}{2}H_2O$: C, 39.10; H, 2.98; N, 13.68. Found: C, 38.64; H, 3.10; N, 13.53.

10*H*-Benzo[*b*]pyridazino[4,5-*e*][1,4]thiazin-1(2*H*)-one (VII)——V or VI (3.0 g.) was heated with 3.0 g. of K_2CO_3 in 50 ml. of dimethylformide under reflux for 8 hr. Filtration of K_2CO_3 followed by evaporation of the filtrate to dryness afforded 2.0 g. of VII. Washing of the product with H_2O, followed by recrystallization from EtOH+H_2O afforded orange crystalls (1.5 g.), m.p. >300°. *Anal.* Calcd. for $C_{10}H_7ON_3S \cdot H_2O$: C, 51.05; H, 3.86; N, 17.86. Found: C, 51.18; H, 3.86; N, 18.26.

Chlorination of VII——A suspention of VII (1.5 g.) in $POCl_3$ (20 ml.) and N,N-dimethylaniline (5 ml.) was refluxed until VII was completely dissolved. This required 3 hr. Excess $POCl_3$ 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 $C_{10}H_6N_3ClS$: 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)-10*H*-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 $C_{16}H_{12}N_4S_2$: 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-10*H*-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 $C_{11}H_8N_3ClS$: C, 52.91; H, 3.21; N, 16.83. Found: C, 52.98; H, 3.40; N, 17.18.

4-(2-Methylaminophenylthio)-10*H*-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, crystalls were separated. The crude product crystallized from $(CH_3)_2CO$ to yield colourless needles (3.5 g.), m.p. 172°. *Anal.* Calcd. for $C_{18}H_{16}N_4S_2$: C, 61.36; H, 4.58; N, 15.90. Found: C, 61.86; H, 4.52; N, 15.85.

4-Methoxy-10*H*-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 H_2O. The precipitated product was collected, washed with H_2O, and dried. Recrystallization from EtOH gave yellow needles (0.8 g.), d.p. 244~246°. *Anal.* Calcd. for $C_{11}H_9ON_3S$: C, 57.14; H, 3.92; N, 18.18. Found: C, 57.07; H, 3.81; N, 17.96.

4-Ethoxy-10*H*-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 $C_{12}H_{11}N_3OS$: C, 58.77; H, 4.52; N, 17.14. Found: C, 58.95; H, 4.35; N, 16.84.

4-Dimethylamino-10*H*-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 H_2O. The separated solid was filtered off and recrystallized from EtOH to yield 0.2 g. of yellow needles, melting 231°(decomp.). *Anal.* Calcd. for $C_{12}H_{12}N_4S$: C, 59.01; H, 4.95; N, 22.94. Found: C, 59.41; H, 5.15; N, 23.04.

1-Ethoxy-10*H*-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 $C_{12}H_{11}N_3OS$: C, 58.77; H, 4.52. Found: C, 58.82; H, 4.49.

2-(2-Dimethylaminoethyl)-10*H*-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 H_2O, 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-10*H*-benzo[*b*]pyridazino[3,4-*e*][1,4]thiazine (II) and 1-chloro-10*H*-benzo[*b*]pyridazino[4,5-*e*][1,4]-thiazine (III). II was converted into 10*H*-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 10*H*-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-10*H*-benzo[*b*]pyridazino[4,5-*e*]-[1,4]thiazin-1(2*H*)-ones were synthesized.

(Received November 9, 1964)