(This ratio varies a little with the operation process). According to the method (2), when Ib was reduced with PtO_2, the ratio was : $\frac{\text{m.p. } 198\sim199^\circ}{\text{m.p. } 156\sim157^\circ}=\frac{1}{5}$ (total yield of picrate is 48.0%) and in the case with Raney Ni, the ratio was $\frac{1}{6.5}$ (total yield is 52.6%).

Free base : Picrate was suspended in 10% KOH solution and then it was extracted with benzene, which was washed with water and desiccated over Na_2SO_4. Evaporation of benzene gave free base in 88.2~90% yield.

Methiodide : A reflux with CH_3I in MeOH for one hour prepared methiodide in quantitative yield.

The authors are very grateful to Chugai Pharmaceutical Co., Ltd. for the elementary analysis and IR measurements.

Summary

Some kinds of simple quinolizidine derivatives were recently found to possess sparteine-like uterus contracting action and this time the new substance with stronger contracting action has been found. Among 3-(subst.-benzyl)-quinolizidine derivatives, 3-(4-chlorobenzyl)-quinolizidine (Ib) was found to be the strongest. Ib showed several folds of activity to sparteine sulfate both *in vitro* and *in vivo* and the toxicity was found to be about one third of it.

The synthesis of Ib was carried out according to the two method (1) and (2), the former synthetic process being found to be beneficial.

(Received October 6, 1965)

[Chem. Pharm. Bull. 14(7) 698~706 (1966)]

UDC 547.855.07

95. Fumio Yoneda, Takayuki Ohtaka, and Yoshihiro Nitta : Pyridazine Derivatives. X.*1 10*H*-Benzo[*b*]pyridazino[3,4-*e*][1,4]thiazine and 5*H*-Benzo[*b*]pyridazino[4,3-*e*][1,4]thiazine.

(*Research Laboratories, Chugai Pharmaceutical Co., Ltd.**2)

In an earlier communication[1] the reaction of 4-(2-amino-phenylthio)-3,6-dichloropyridazine with hydrochloric acid has been shown to give 3-chloro-5*H*-benzo[*b*]pyridazino[4,3-*e*][1,4]thiazine (3,4-diazaphenothiazine type) as well as 3-chloro-10*H*-benzo[*b*]pyridazino[3,4-*e*][1,4]thiazine (1,2-diazaphenothiazine type) originally claimed.[2] This novel entry into 3,4-diazaphenothiazine system prompted us to look more closely into synthetic methods for these preparations and also to investigate the mechanism of these reactions by a molecular orbital method. In the present paper we report the details of some of our investigations.

Treatment of 3,4,6-trichloropyridazine with 2-aminothiophenol in methanolic potassium hydroxide solution yielded 4-(2-aminophenylthio)-3,6-dichloropyridazine (I). In this case, proof of the structure of I was obtained from the fact that the condensation of 4-bromo-3,6-dichloropyridazine (II) with 2-aminothiophenol gave the same

---

*1 Part IX : Yakugaku Zasshi, in press.

*2 Takataminami-cho, Toshima-ku, Tokyo (米田文郎, 大高孝之, 新田義博).

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

2) J. Druey : Angew. Chem., **70**, 5 (1958).

product (I). II was prepared by bromination of 4-hydrazino-3,6-dichloropyridazine with hydrobromic acid and sodium hypobromite, although II could be obtained by neither chlorination of 4-bromomaleic hydrazide[3] with phosphoryl chloride nor diazotization of 4-amino-3,6-dichloropyridazine in hydrobromic acid.

Compound (I) was treated with dilute alcoholic hydrochloric acid or acetic acid and heated to 90~100°. After a few minutes yellow crystals began to deposit, and after 2 hr. a excellent yield of compound (III), m.p. 268° (decomp.), was obtained. A molecular formula of $C_{10}H_6N_3ClS$ was assigned to III, based on the elementary analysis and molecular weight measurement. This formation of III from I was accompanied by a small amount of golden needles (V) that melted with decomposition at 278° and gave good analyses for $C_{10}H_6N_3ClS$, whose structure will be described below.

The infrared spectrum of III was very similar with that of 4-amino- or 4-anilino-3,6-disubstituted pyridazine and also very different from those of 1,2-diazaphenothiazines. From these facts and considering the mode of formation, compound (III) was supported to be 3-chloro-5*H*-benzo[*b*]pyridazino[4,3-*e*][1,4]thiazine which appeared to be formed through an rearranged intermediate, 4-(2-mercaptoanilino)-3,6-dichloropyridazine (not isolated). When I was heated in only alcohol for much longer periods, compound (III) was also obtained.

We sought evidence of rearranged intermediate, 4-(2-mercaptoanilino)-3,6-dichloropyridazine, that might have been present in the conversion of I to III, but found none in the ultraviolet absorption spectra of samples withdrawn at various intervals and a smooth transition from the spectrum of starting material to that of III was observed.

Reaction of I with sodium methoxide or methanolic potassium hydroxide did not produce III, but gave 4-(2-aminophenylthio)-3-methoxy-6-chloropyridazine (IV), whose infrared spectrum showed the existence of a typical primary amino group. IV was converted into III using the same method as that for preparing III from I. Therefore, the above-mentioned rearrangement reaction leading into 3,4-diazaphenothiazine presents a different appearance from the base-catalyzed Smiles rearrangement.[4]

I on treatment with concentrated hydrochloric acid afforded only the compound (V) in good yield, but no III was obtained. V was also obtained by heating I on the absence of solution : I on heating at 140~150° reacted suddenly and gave red crystals (VI) which showed no definite melting point and changed to black from red at 250~260°. VI was easily converted to V on treating with alcohol or water as well as alkali solution, and reversely V to VI by treatment with concentrated hydrochloric acid. Therefore VI is chlorohydrate of V.

Attempts to obtain the desulfurization product of V with Raney nickel W 2 were unsuccessful recovering III unchanged. However, the desulfurization of V with Raney nickel prepared according to Mozingo's method[5] gave colorless crystals (VII), $C_{10}H_8N_2$ in poor yield. Treatments of 10*H*-benzo[*b*]pyridazino[3,4-*e*][1,4]thiazine, 3-anilinopyridazine and 3-anilino-6-chloropyridazine with Raney nickel described above afforded the same desulfurization product (VII). VII was also obtained on hydrogenation of 3-anilinopyridazine in the presence of Raney nickel W 2 under warming. From these data it seemed likely that 3-anilinopyridazine introduced by dechlorination and desulfurization of V was further reduced into an intermediate compound (VIII) and the latter was cyclized to 2-anilino-2-pyrroline (VII) involving elimination of ammonia. The nuclear magnetic resonance spectrum of VII is in excellent accord with a assigned structure : the multiplets centering about 6.5τ and 7.7τ are due to the methylene hydrogens of

3) Yu. A. Baskakov, N. N. Mel'nikov : Zhur. Obshchei. Khim., **24**, 1216 (1954).
4) Recently the acid catalyzed Smiles rearrangement was reported : O. R. Rodig, R. E. Collier, R. K. Schlatzer: J. Org. Chem., **29**, 2652 (1964); Y. Maki, *et al.* : Yakugaku Zasshi, **85**, 429 (1965).
5) Mozingo, *et al.* : J. Am. Chem. Soc., **65**, 1013 (1943).

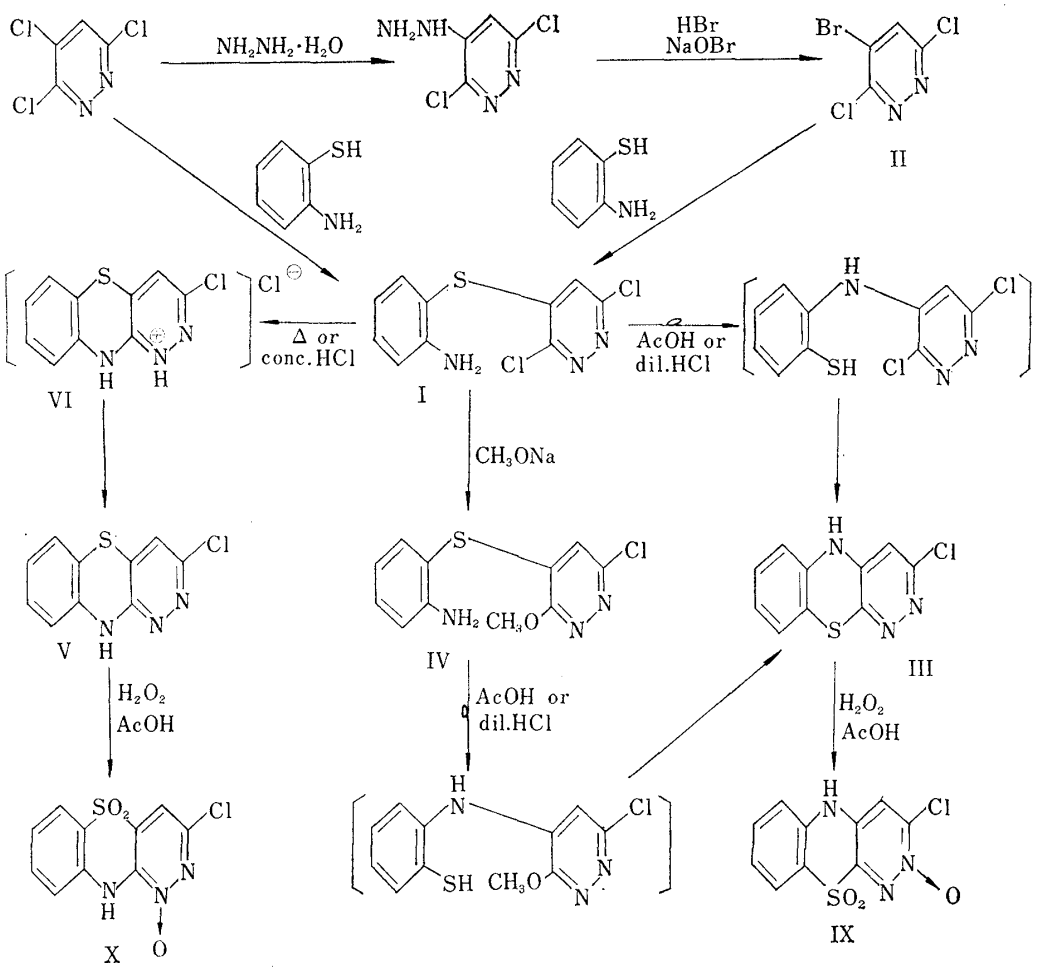

Chart 1.

pyrroline ring, the anilino NH absorbs at 5.3τ, and the hydrogen of NH group of pyrroline ring appears at 8.8τ (triplet, J~7 c.p.s.). Thus the structure of V was confirmed to be 3-chloro-10*H*-benzo[*b*]pyridazino[3,4-*e*][1,4]thiazine. To our knowledge, few examples of reductive ring contraction to pyrrole system of condensed pyridazine system have been reported[6] and in no instance does that to pyrrole of single pyridazine ring occur under such conditions as are reported here.

The action of hydrogen peroxide in acetic acid on III and V resulted in oxidation without desulfurization, whereas oxidative decomposition of 1-azaphenothiazine[7] with hydrogen peroxide is known to give 2-anilinopyridine. These oxidative products drived from III and V were supported to be trioxides (IX and X), respectively, based on the elementary analyses and the infrared spectra [IX; ν as (SO_2)=1337 cm^{-1}, νs (SO_2)=1152 cm^{-1} and ν_{N-O}=1313 cm^{-1}. X; ν as (SO_2)=1307 cm^{-1}, νs (SO_2)=1115 cm^{-1} and ν_{N-O}=1307 cm^{-1}].

When 3,4,6-trichloropyridazine was treated with 2-methyl-aminothiophenol introduced from 3-methyl-2(3*H*)-benzothiazolinone in alcoholic potassium hydroxide solution, 4-(2-methylaminophenylthio)-3,6-dichloropyridazine (XI) was obtained. XI was more reactive than I and converted easily into 3-chloro-5-methyl-5*H*-benzo[*b*]pyridazino[4,3-*e*][1,4]thiazine (XII) by treating with alcohol or glacial acetic acid. XI on treatment with

6) S. Gabriel, G. Eschenbach: Ber., **30**, 3022 (1897); S. Gabriel, A. Neumann: *Ibid.*, **26**, 521, 705 (1893); A. Doube: *Ibid.*, **38**, 206 (1905); J.C.E. Simpson: "Condensed Pyridazine and Pyrazine Rings," Interscience, New York, 10 (1953).

7) A.R. Gennaro: J. Org. Chem., **24**, 1156 (1959).

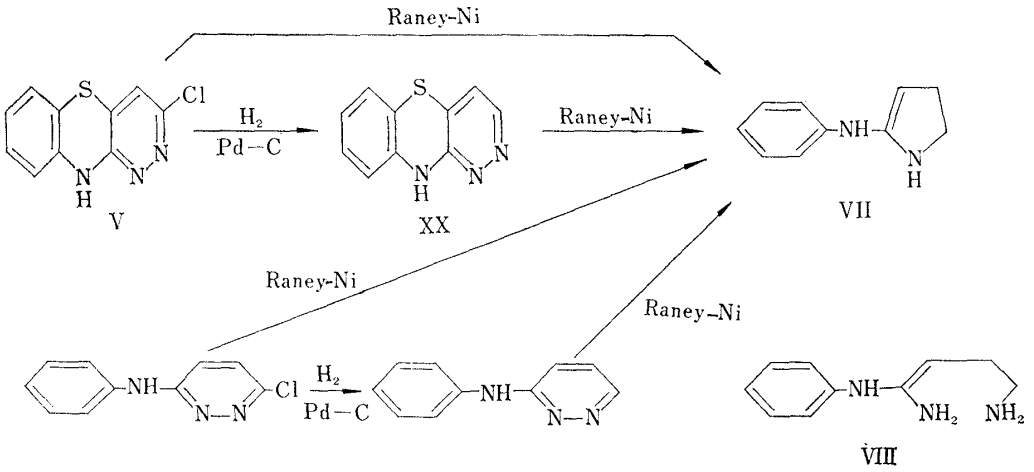

Chart 2.

concentrated hydrochloric acid yielded 3-chloro-10-methyl-10*H*-benzo[*b*]pyridazino[3,4-*e*][1,4]thiazine (XIII). Proof of the structures of XII and XIII was obtained from the fact that their ultraviolet spectra[8] were nearly identical with those of III and V, respectively.

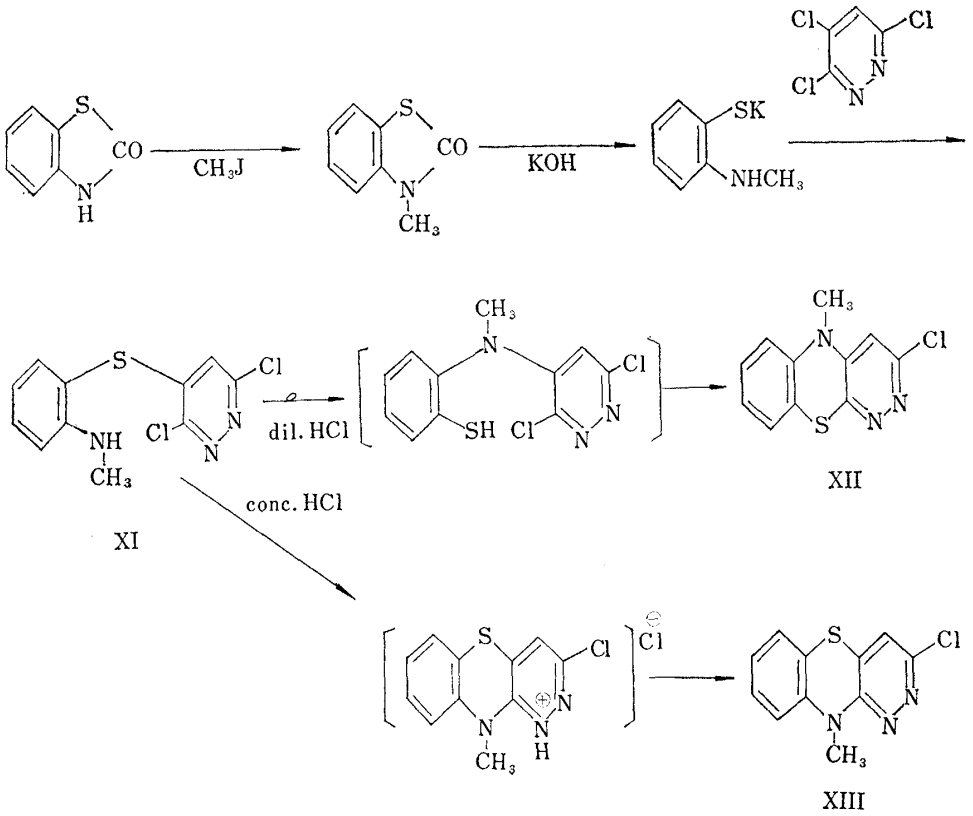

Chart 3.

3-Methoxy-5*H*-benzo[*b*]pyridazino[4,3-*e*][1,4]thiazine (XIV) was prepared by heating III under pressure with sodium methoxide in methanol and 3-dimethylamino-5*H*-benzo[*b*]pyridazino[4,3-*e*][1,4]thiazine (XV) was obtained by heating III under pressure with dimethylamine in alcohol. In a similar way V was converted to 3-methoxy-(XVI) and 3-dimethylamino-10*H*-benzo[*b*]pyridazino[3,4-*e*][1,4]thiazine (XVII). 3-methoxy-5-Methyl-5*H*-benzo[*b*]pyridazino[4,3-*e*][1,4]thiazine (XVIII) and 3-methoxy-10-methyl-10*H*-benzo[*b*]pyridazino[3,4-*e*][1,4]thiazine (XIX) are synthesized from XII and XIII with sodium methoxide

8) F. Yoneda, T. Ohtaka, Y. Nitta : This Bulletin, **13**, 580 (1965).

in the same condition as above. Furthermore, catalytic hydrogenation of V over palladium charcoal gave 10*H*-benzo[*b*]pyridazino[3,4-*e*][1,4]-thiazine (XX), whereas attempts to obtain dechlorinated III in the similar hydrogenation was unsuccessful and III was recovered unchanged. Acetylation of III and V with acetic anhydride and anhydrous sodium acetoxide afforded 5-acetyl-III (XXI) and 10-acetyl-V (XXII), respectively, which were easily hydrolized into III and V with alkali or acid.

Discussion

The π-electron distributions, the superdelocalizabilities and the delocalization energies using a molecular orbital method were calculated in order to find a clue of the mechanism of the aforesaid reactions. The results of calculations were shown in Figs. 1 and 2.*3

In the compound (1), as can be seen from Fig. 1, the electron density at the 4 position is the smallest of those at the positions 3,4 and 5 and also the superdelocalizability for the nucleophilic reaction ($S\gamma^{(N)}$) is the greatest in this position. This is in excellent accord with the experimental result that the 4-position of (1) is most reactive for nucleophilic attack and (1) on treating with o-aminothiophenol gives (2).

In compound (2), the 4 position has less density of π-electron than the 3 position and moreover $S_4^{(N)}$ (=1.1082) is greater than $S_3^{(N)}$ (=0.9741). The result of this calculations can elucidate reasonably the experimental behavior that the amino group in (2) might attack predominantly toward the 4-position and consequently occur intramolecular rearrangement to give (3). The fact that in (2) $S_4^{(N)}$ is greater than $S_3^{(N)}$ suggests that the activation energy to take such a five-mem-bered cyclic transition state as Fig. 2 A is lower than that to take such a six-membered cyclic transition state as Fig. 2 B and accordingly the rearrangement through Fig. 2 A might occur predominantly.

Moreover, molecular orbital calculations indicate that the delocalization energy of (3) (6.0334 β) is greater by ca. 12.5 Kcal./mole than that of (2) (5.4082 β). Assuming that the angle-strain energy of the two compounds is nearly equal, there would appear to be driving force for this rearrangement. In this way the success or failure and the hardness or ease in the well known Smiles rearrangement might be predicted from the calculations of nucleophilic reactivity and delocalization energy.

In the electron density of the rearranged product (3) (not isolated), the 3 position (q_3=1.020) is greater than the 4 position (q_4=0.944) and this is not in agreement with the experimental result. However, the $S\gamma^{(N)}$ having closer relation to the nucleophilic substitution supported the experimental result; $S_3^{(N)}$ (=0.9469) $>S_4^{(N)}$ (=0.8908). Thus, the SH-group in (3) would attack toward 3 position giving (4).

*3 Calculations were made by means of the simple LCAO-MO method neglecting overlap. The parameters of the coulomb and resonance integrals for substituent groups are as follows :

Substituent X	a_x [a]	a_r [b]	l [c]
-Cl	1.8	0.18	0.8
=N-	0.6	0.1	1
$=\overset{+}{N}H-$	2	0.2	1
$-N<$	1	0.1	1
-NH	0.4	0	0.6
-S-	0.9	0.1	0.5
-SH-	0.55	0	0.6

a) coulomb integral of the substituent X : $\alpha_x=\alpha+a_x\beta$.
b) coulomb integral of the carbon atom adjacent to X : $\alpha_{adj}=\alpha+a_r\beta$.
c) resonance integral between that carbon atom and X : $\beta_{c-x}=l\beta$.

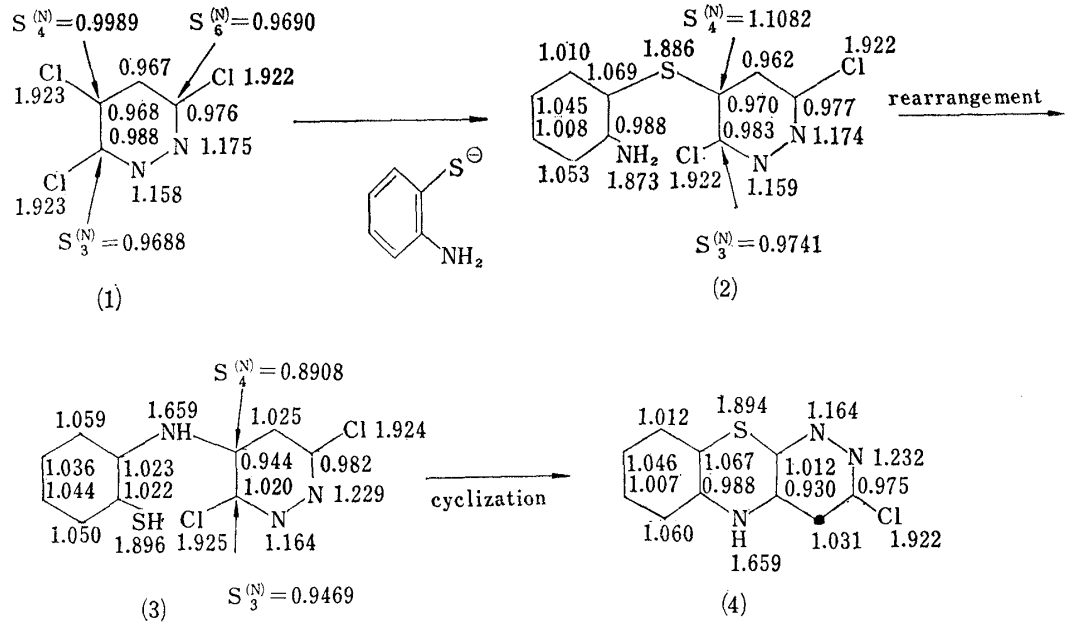

Fig. 1.

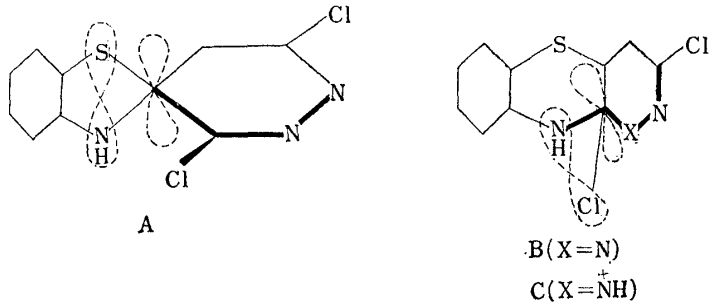

Fig. 2. Transition states based on the frontier electronic theory. Pyridazine ring and benzene ring are virtually perpendicular to each other. Dotted lines represent pseudo π-orbitals.

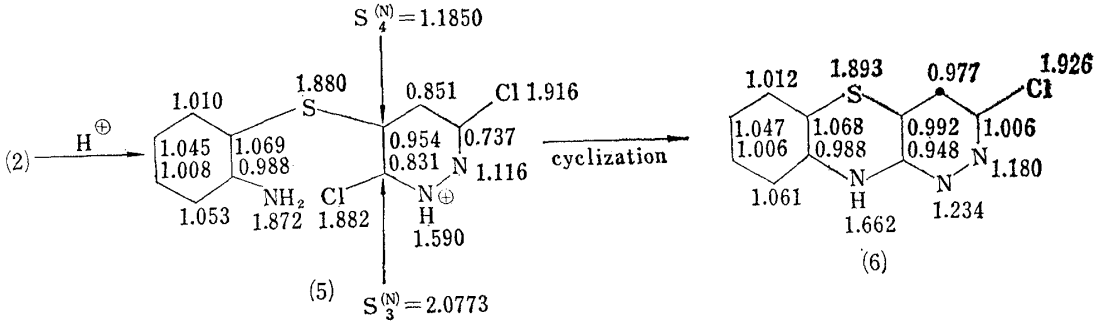

Fig. 3.

The fact that (2) on treatment with concentrated hydrochloric acid afford (6) can be explained by the protonation of the nitrogen atom at the 2 position of (2). If the nitrogen at the 2 position is protonated, as is seen from (5) of Fig. 3, the electron density of 3 position (q_3=0.831) becomes less than that of 4 position (q_4=0.954) and also $S_3^{(N)}$ (=2.0 773) becomes greater than $S_4^{(N)}$ (=1.1850). Consequently the amino group would attack predominantly toward the 3-position and the ring closure might take place through a six-membered transition state (Fig. 2 C) to give (6).

It is worthy to note that both (4) and (6) here obtained have one proton in 1 and 4

positions in pyridazine ring respectively and the electron density at the 1 position of (4) is excessive (q_1=1.031) and that at the 4 position of (6) is deficient (q_4=0.977). Therefore, the nuclear magnetic resonance spectra of (4) and (6) is of considerable interest with regard to theories of chemical shifts in nuclear magnetic resonance spectroscopy. Recently the nuclear magnetic resonance spectra of aromatic hydrocarbons and aromatic hetero rings have indicated that their proton chemical shifts are proportional to their charge densities and that the differential effects of ring currents of π-electrons appears to be insignificant.[9~12] In case of (4) and (6), the proton of pyridazine ring in (4) might perhaps show chemical shift in higher field than that in (6), assuming that in the two compounds the magnetic anisotropic effect of adjacent chlorine atom is nearly equal and that of ring nitrogen is neglected. Significantly, the obserbed chemical shifts of (4) and (6) (Fig. 4) supported the above mentioned prediction.

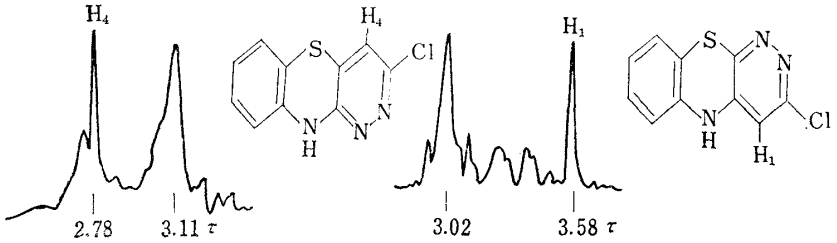

Fig. 4. Nuclear Magnetic Resonance Spectra of (4) and (6) in Dimethylsulfoxide at a Frequency of 60 Mc.

Experimental*4

4-(2-Aminophenylthio)-3,6-dichloropyridazine (I)——A solution 25.4 g. of 2-aminothiophenol and 13.1 g. of KOH in 400 ml. of MeOH was added dropwise to a stirred solution of 36 g. of 3,4,6-trichloropyridazine in 200 ml. of MeOH. During the addition the product began to separate as a pale yellow solid. The mixture was stirred for 4 hr. at room temperature and then filtered to give 40 g. of 4-(2-aminophenylthio)-3,6-dichloropyridazine as a pale yellow solid. The analytical sample was prepared in the form of pale yellow needles, (d.p. ca. 150°) by recrystallization from MeOH. *Anal.* Calcd. for $C_{10}H_7N_3Cl_2S$: C, 44.12; H, 2.57; N, 15.44. Found: C, 44.17; H, 2.71; N, 15.71.

3-Chloro-5*H*-benzo[*b*]pyridazino[4,3-*e*][1,4]thiazine (III)——a) A mixture of 35.0 g. of I and 1500 ml. of AcOH was heated for 2 hr. in a water bath at 90°. During this time, the starting material dissolved, followed by the appearance of a yellow solid. The mixture was cooled and the yellow solid was collected by filtration, giving 28 g. of 3-chloro-5*H*-benzo[*b*]pyridazino[4,3-*e*][1,4]thiazine. Recrystallization from EtOH gave yellow powders, m.p. 268° (decomp.). *Anal.* Calcd. for $C_{10}H_6N_3ClS$: C, 50.96; H, 2.55; N, 17.83. Found: C, 51.40; H, 2.60; N, 17.81.

b) I (0.5 g.) was added to 300 ml. of EtOH and heated at the boiling point for 24 hr. The mixture was cooled and filtered, yielding 0.35 g. of III, m.p. 268°(decomp.), identified by comparison of its infrared spectrum with that of an authentic sample.

c) A mixture of 0.5 g. of IV and 20 ml. of AcOH was heated for 1 hr. at 90°. On standing, 0.3 g. of III crystallized, m.p. 259°(decomp.), the structure of which was confirmed by comparison of its infrared spectrum with that of an authentic sample. A recrystallization from EtOH raised the melting point to 268° (decomp.).

4-Bromo-3,6-dichloropyridazine (II)——A 2*M* solution of NaOBr was prepared by the addition of Br_2 (16 g.) to a solution of NaOH (10 g.) in H_2O followed by dilution to 50 ml.

4-Hydrazino-3,6-dichloropyridazine (1.79 g.) was dissolved in constant boiling HBr (110 ml.). After the addition of the NaOBr solution (50 ml.) prepared above, an excess of a 25% solution of NaOH was added in

*4 All melting points are uncorrected. Microanalyses were performed by the Analysis Room of this laboratory. Where appropriate, identity of compounds was confirmed by comparison of infrared spectra determined in KBr discs on a Hitachi EPI 2. All NMR spectra were recorded on a Varian A-60 instrument.

9) G. Fraenkel, *et al.*: J. Am. Chem. Soc., **82**, 5846 (1960).
10) T. Schaffer, W. G. Schneider: Can. J. Chem., **41**, 966 (1963).
11) T. J. Katz, P. T. Garratt: J. Am. Chem. Soc., **86**, 5198 (1964).
12) Y. Kawazoe, S. Natsume: Yakugaku Zasshi, **83**, 525 (1963).

cooling. The precipitate was filtered off, washed with H_2O, dried over KOH *in vacuo*, and purified by vacuum sublimation to give colorless needles (1.5 g.), m.p. 80~81°. *Anal.* Calcd. for $C_4HN_2BrCl_2$: C, 21.08; H, 0.44; N, 12.29. Found: C, 20.78; H, 0.68; N, 12.23.

4-(2-Aminophenylthio)-3-methoxy-6-chloropyridazine (IV)——I (2.7 g.) was refluxed in 30 ml. MeOH containing 0.3 g. of Na for 1 hr. After evaporation of solvent, the residue was diluted with H_2O. The separated solid was filtered off and recrystallized from MeOH to yield 1.6 g. of pale yellow needles, melting 133°(decomp.). *Anal.* Calcd. for $C_{11}H_{10}ON_3ClS$: C, 49.35; H, 3.74; N, 15.70. Found: C, 49.41; H, 3.72; N, 15.76.

3-Chloro-10*H*-benzo[*b*]pyridazino[3,4-*e*][1,4]thiazine (V)——a) A mixture of 40 g. of I and 700 ml. of conc. HCl was heated at 90°. The color of the reaction mixture changed to a brown, and after 3 hr. of heating, dark red crystals of 3-chloro-10*H*-benzo[*b*]pyridazino[3,4-*e*][1,4]thiazine chlorohydrate (VI) began to appear. The dark mixture was diluted with aq. ammonia, whereby it turned yellow. The solid which formed was collected by filtration, washed with water, and recrystallized from toluene, yielding 20 g. of 3-chloro-10*H*-benzo[*b*]pyridazino[3,4-*e*][1,4]thiazine (V) as yellow needles, m.p. 278°. *Anal.* Calcd. for $C_{10}H_6N_3ClS$: C, 50.96; H, 2.55; N, 17.83. Found: C, 50.93; H, 2.49; N, 17.90.

b) I (1 g.) was heated in an oil bath at 150° for 1 hr., after which time red solid was added with aq. ammonia. The yellow solid was collected by filtration, washed with water, and recrystallized from toluene, yielding 0.5 g. of V as yellow needles, m.p. 278°, identified by comparison of its infrared spectrum with that of an authentic sample.

Desulfurization of 10*H*-benzo[*b*]pyridazino[3,4-*e*][1,4]thiazine (XX)——10*H*-Benzo[*b*]pyridazino[3,4-*e*]-[1,4]thiazine (0.7 g.), Raney nickel, prepared according to Mozingo's method, (20 g.) and EtOH (100 ml.) were heated under refluxed for 4 hr. and the mixture was filtered. The Raney nickel residue was washed twice with hot EtOH. The alcoholic solution was concentrated and the oily residue was purified by chromatography on alumina with $CHCl_3$ as eluent. Concentration of the pale yellow eluate afforded 0.1 g. of colorless needles. Recrystallization from petroleum ether gave 2-anilino-2-pyrroline (VII) as colorless needles, m.p. 110°. *Anal.* Calcd. for $C_{10}H_{12}N_2$: C, 74.96; H, 7.55; N, 17.49. Found: C, 75.03; H, 7.48; N, 17.56.

Desulfurization of V——V (2.0 g.) was treated with Raney nickel described above (30 g.) in EtOH (300 ml.) in a similar way to give 0.2 g. of 2-anilino-2-pyrroline (VII), m.p. 110°, identified by comparison of its infrared spectrum with that of an authentic sample.

Desulfurization of 3-Anilinopyridazine——By the same procedure described above, 3-anilinopyridazine (1.0 g.) yielded 0.1 g. of 2-anilino-2-pyrroline (VII), m.p. 110°.

10*H*-Benzo[*b*]pyridazino[3,4-*e*][1,4]thiazine (XX)——A solution of V (2.0 g.) in 500 ml. of EtOH was hydrogenated over Pd-C (10%, 0.5 g.) until 190 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 added with aq. ammonia. The yellow solid which formed was collected by filtration, washed with H_2O, and recrystallized from EtOH, yielding 1 g. of 10*H*-benzo[*b*]pyridazino[3,4-*e*][1,4]thiazine as pale yellow needles, m.p. 263°. *Anal.* Calcd. for $C_{10}H_7N_3S$: C, 59.70; H, 3.51; N, 20.89. Found: C, 59.84; H, 3.74; N, 21.07.

4-Anilino-3,6-dichloropyridazine——A solution of 3.6 g. of 3,4,6-trichloropyridazine and 1.9 g. of aniline in 50 ml. of EtOH was refluxed for ca. 3 hr. After evaporation of solvent, the residue was recrystallized from EtOH+H_2O to yield 2.5 g. of 4-anilino-3,6-dichloropyridazine as colorless needles, m.p. 140°. *Anal.* Calcd. for $C_{10}H_7N_3Cl_2$: C, 50.17; H, 3.23; N, 17.69. Found: C, 50.02; H, 2.94; N, 17.50.

3-Chloro-5*H*-benzo[*b*]pyridazino[4,3-*e*][1,4]thiazinetrioxyde (IX)——A mixture of 1 g. of III, 10 ml. of 30% H_2O_2, and 100 ml. of AcOH was heated on a steam bath. After a short time, the starting material dissolved, and the color of the reaction mixture changed from a brown to a yellow. After 1 hr. AcOH was evaporated *in vacuo* and the residue was recrystallized from DMF+H_2O, yielding 1 g. of yellow powders, m.p. 190° (decomp.). *Anal.* Calcd. for $C_{10}H_6O_3N_3ClS$: C, 42.33; H, 2.12; N, 14.81. Found: C, 42.84; H, 2.33; N, 14.63.

3-Chloro-10*H*-benzo[*b*]pyridazino[3,4-*e*][1,4]thiazinetrioxyde (X)——V (2 g.) was added to 100 ml. AcOH containing 10 ml. of 30% H_2O_2 and treated as described for IX to give yellow solid (2 g.).

The crude product crystallized from AcOH to yield yellow needles, m.p. 276° (decomp.). *Anal.* Calcd. for $C_{10}H_6N_3O_3ClS$: C, 42.33; H, 2.12; N, 14.81. Found: C, 42.63; H, 2.42; N, 14.61.

3-Methyl-2(3*H*)-benzothiazolinone——2(3*H*)-Benzothiazolinone (2.3 g.) was dissolved in 50 ml. EtOH containing 0.36 g. of Na. To this solution, 2.3 g. of CH_3I was added and refluxed for 2 hr. After evaporation of EtOH, the residue was diluted with H_2O to give precipitate, which on recrystallization from MeOH +H_2O gave colorless needles (1.4 g.), m.p. 72°. *Anal.* Calcd. for C_8H_7ONS: C, 58.18; H, 4.27; N, 8.48. Found: C, 58.09; H, 4.24; N, 8.44.

4-(2-Methylaminophenylthio)-3,6-dichloropyridazine (XI)——3-Methyl-2(3*H*)-benzothiazolinone (1.4 g.) was added to 20 ml. EtOH containing 1 g. of KOH and refluxed for 1 hr. To this reaction mixture, a solution of 1.6 g. of 3,4,6-trichloropyridazine in 30 ml. of EtOH was added dropwise under stirring and cooling. After stirring for 1 hr. at room temperature, the reaction solution was concentrated *in vacuo* and the residue was diluted with H_2O. The separated yellow solid was filtered and recrystallized from EtOH to give 1 g. of pale yellow prisms, d.p. ca. 120°. *Anal.* Calcd. for $C_{11}H_9N_3Cl_2S$: C, 46.18; H, 3.17; N, 14.69.

Found: C, 46.09; H, 3.13; N, 14.53.

3-Chloro-5-methyl-5*H*-benzo[*b*]pyridazino[4,3-*e*][1,4]thiazine (XII)——A mixture of 1 g. of XI, 1 ml. of conc. HCl and 30 ml. of EtOH was heated for 0.5 hr. in a water bath at 90°. The reaction mixture was cooled and the separated yellow crystals was collected. Recrystallization from MeOH gave 0.5 g. of pale needles, m.p. 210°. *Anal.* Calcd. for $C_{11}H_8N_3ClS$: C, 52.92; H, 3.23; N, 16.83. Found: C, 53.11; H, 3.21; N, 16.94.

3-Chloro-10-methyl-10*H*-benzo[*b*]pyridazino[3,4-*e*][1,4]thiazine (XIII)——XI (0.5 g.) was added to 20 ml. of conc. HCl and heated for 1 hr. at 90°. The reaction mixture was diluted with H_2O and neutralized with Na_2CO_3 to give yellow precipitate, which on recrystallization from EtOH gave 0.3 g. of yellow needles, m.p. 170°. *Anal.* Calcd. for $C_{11}H_8N_3ClS$: C, 52.92; H, 3.23; N, 16.83. Found: C, 53.01; H, 3.39; N, 16.79.

3-Methoxy-5*H*-benzo[*b*]pyridazino[4,3-*e*][1,4]thiazine (XIV)——III (0.5 g.) was heated in 30 ml. MeOH containing 0.1 g. of Na in a sealed tube for 4 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 (0.3 g.), m.p. 268°. *Anal.* Calcd. for $C_{11}H_9ON_3S$: C, 57.14; H, 3.92; N, 18.18. Found: C, 57.47; H, 3.61; N, 18.22.

3-Methoxy-10*H*-benzo[*b*]pyridazino[3,4-*e*][1,4]thiazine (XVI)——V (0.5 g.) was added to 30 ml. MeOH containing 0.1 g. of Na and treated in the same way as described above to give yellow needles (0.4 g.), m.p. 235°. *Anal.* Calcd. for $C_{11}H_9ON_3S$: C, 57.14; H, 3.92; N, 18.18. Found: C, 57.37; H, 3.58; N, 18.20.

3-Dimethylamino-5*H*-benzo[*b*]pyridazino[4,3-*e*][1,4]thiazine (XV)——III (0.7 g.) was heated in 100 ml. EtOH containing excess dimethylamine in a sealed tube for 5 hr. at 140°. After evaporation of solvent, the residue was diluted with H_2O. The separated solid was filtered and recrystallized from acetone to yield 0.5 g. of yellow crystals, m.p. 275°. *Anal.* Calcd. for $C_{12}H_{12}N_4S$: C, 59.01; H, 4.95; N, 22.94. Found: C, 59.24; H, 4.92; N, 22.93.

3-Dimethylamino-10*H*-benzo[*b*]pyridazino[3,4-*e*][1,4]thiazine (XVII)——V (0.5 g.) was added to 100 ml. EtOH containing excess dimethylamine and treated as described above to give yellow solid (0.3 g.). Recrystallization from EtOH gave an analytical sample as yellow prisms, m.p. 285° (decomp.). *Anal.* Calcd. for $C_{12}H_{12}N_4S$: C, 59.01; H, 4.95; N, 22.94. Found: C, 58.97; H, 4.84; N, 22.79.

3-Methoxy-5-methyl-5*H*-benzo[*b*]pyridazino[4,3-*e*][1,4]thiazine (XVIII)——XII (0.3 g.) was heated in 30 ml. MeOH containing 0.1 g. of Na in a sealed tube for 4 hr. at 120°. After evaporation of MeOH, the residue was diluted with H_2O. The separated solid was filtered and recrystallized from EtOH to yield 0.2 g. of pale yellow needles, m.p. 137°. *Anal.* Calcd. for $C_{12}H_{11}ON_3S$: C, 58.77; H, 4.52; N, 17.14. Found: C, 59.01; H, 4.53; N, 16.99.

3-Methoxy-10-methyl-10*H*-benzo[*b*]pyridazino[3,4-*e*][1,4]thiazine (XIX)——XIII 0.3 g. was added to 30 ml. MeOH containing 0.1 g. of Na and treated as described for XVIII to give yellow crystals (0.2 g.). Recrystallization from acetone gave an analytical sample as pale yellow needles, m.p. 175°. *Anal.* Calcd. for $C_{12}H_{11}ON_3S$: C, 58.77; H, 4.52; N, 17.14. Found: C, 58.61; H, 4.48; N, 17.29.

3-Chloro-5-acetyl-5*H*-benzo[*b*]pyridazino[4,3-*e*][1,4]thiazine (XXI)——A mixture of 2 g. of III, 10 ml. of Ac_2O, and 0.2 g. of anhydrous sodium acetate was refluxed for 1 hr. The reaction mixture was diluted with a large amount of water. The solid which formed was collected by filtration, giving 2 g. of the acetylated III as colorless needles, m.p. 166°. Recrystallization from MeOH did not change the melting point. *Anal.* Calcd. for $C_{12}H_8ON_3ClS$: C, 52.28; H, 3.10. Found: C, 52.34; H, 2.96.

3-Chloro-10-acetyl-10*H*-benzo[*b*]pyridazino[3,4-*e*][1,4]thiazine (XXII)——A mixture of 2 g. of V, 10 ml. of Ac_2O, and 0.2 g. of anhydrous sodium acetate was treated as described for XXI to give 2 g. of 3-chloro-10-acetyl-10*H*-benzo[*b*]pyridazino[3,4-*e*][1,4]thiazine as colorless needles, m.p. 151~152°. *Anal.* Calcd. for $C_{12}H_8ON_3ClS$: C, 52.28; H, 3.10; N, 14.97. Found: C, 51.91; H, 2.90; N, 15.13.

The authors would express their deep gratitude to Dr. C. Nagata, Chief of Department of Biological Physics, the National Cancer Center Research Institute, for kind guidance in quantum chemical consideration and also to Dr. T. Akiba, Director of this laboratory for his encouragement throughout the course of this work.

Summary

4-(2-Aminophenylthio)-3,6-dichloropyridazine (I) on treating with dil. hydrochloric acid or acetic acid gave 3-chloro-5*H*-benzo[*b*]pyridazino[4,3-*e*][1,4]thiazine (3,4-diazaphenothiazine type) through rearrangement and cyclization. 3-Chloro-10*H*-benzo[*b*]pyridazino-[3,4-*e*][1,4]thiazine (1,2-diazaphenothiazine type) was obtained by either heating of I at 150° or treating of I with conc. hydrochloric acid through direct cyclization. The mechanism of the aforesaid reactions was discussed using a molecular orbital method. Several 1,2- and 3,4-diazaphenothiazine derivatives were synthesized.

(Received November 5, 1965)