18. **Torizo Takahashi and Yoshifumi Maki**: Sulfur-containing Pyridine Derivatives. XLIII.[1] Synthesis of Pyrido[2,3:2′,3′]-*p*-thiazines. (2).

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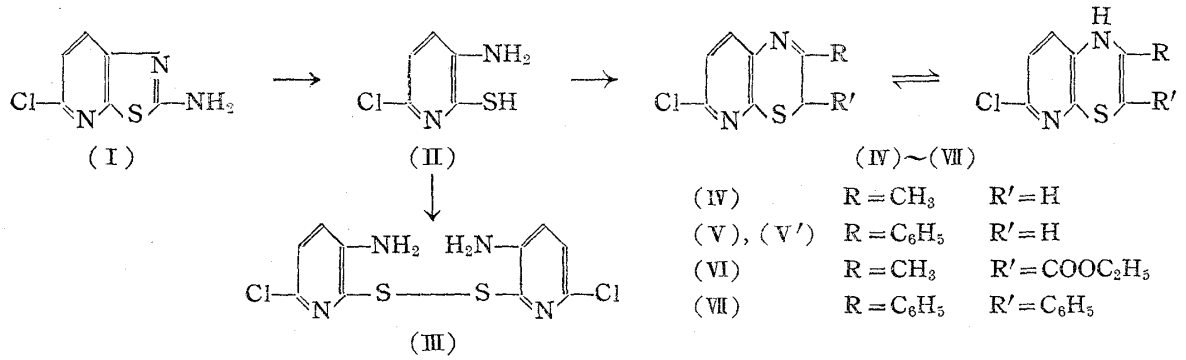
The preceding paper[1] reported the syntheses of derivatives of 6-ethoxypyrido[2,3 : 2′,3′]-*p*-thiazine. The present communication describes the syntheses of derivatives of 6-chloropyrido[2,3 : 2′,3′]-*p*-thiazine and pyrido[3,4 : 3′,2′]-*p*-thiazine, and some of their chemical properties, especially their behavior to acids and alkalis.

The key intermediate of the present investigation was 2-mercapto-3-amino-6-chloropyridine[2] (II) in the place of 2-mercapto-3-amino-6-ethoxypyridine used in the previous case. The preparation of these was carried out by the alkaline hydrolysis of 6-chloro-2-aminopyrido[2,3 : 5′,4′]thiazole (I) using either barium hydroxide (product IIb) or sodium hydroxide (product IIs). The use of the latter method was found to be unfavorable in the purity of (II), as purification of (II) was impossible through recrystallization owing to its sensitivity to oxidation and impurities contaminating (II) caused an undesirable side reaction as the following facts show.

In the alkylation of (IIs) with alkyl halides none of the expected thioether but unidentified high melting substance[3] was always obtained. On the other hand, however, the use of (IIb) gave corresponding pyridyl alkyl thioether in a good yield, some of which will appear in the succeeding issues of this Bulletin. The same phenomenon giving rise to an unknown substance by the use of (IIs) was also encountered in the present experiments for the preparation of 6-chloropyrido[2,3 : 2′,3′]-*p*-thiazines (IV～VII). To take an example of 6-chloro-5′-phenylpyrido[2,3 : 2′,3′]-*p*-thiazine (V),** usage of (IIs) afforded mainly an unknown product as colorless needles of m.p. 225°, insoluble in organic solvents except hot ethanol, together with a small amount of the desired product (V).

2-Mercapto-3-amino-6-chloropyridine faded to brown in the air and was easily oxidized in hot ethanol to form 3,3′-diamino-6,6′-dichlorodipyridyl 2,2′-disulfide (III) crystallizing in orange rhombics, m.p. 210°(decomp.), which Takahashi and Yamamoto[2] reported before as a light yellow crystalline powder, m.p. 229～230°(decomp.). This was occasionally accompanied as a by-product owing to autoxidation in the following experiments starting from (II).



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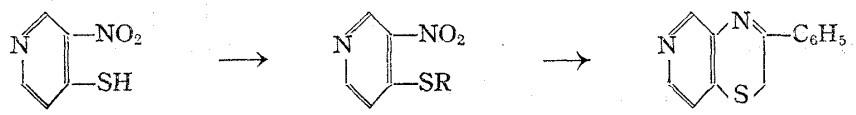
** See also the reaction of crude 2-mercapto-3-amino-6-ethoxypyridine with phenacyl bromide appearing in the previous paper.

1) Part XLII : This Bulletin, **2**, 382 (1954).
2) T. Takahashi, Y. Yamamoto : J. Pharm. Soc. Japan, **71**, 916(1951).
3) T. Takahashi, K. Ueda : *Ibid.*, **73**, 442(1953).

Condensation of (II) with some α-halocarbonyls, including bromoacetone, phenacyl bromide, ethyl α-chloroacetoacetate, and chlorodesoxybenzoin afforded 6-chloro-5′-methylpyrido[2,3 : 2′,3′]-*p*-thiazine (IV), 6-chloro-5′-phenylpyrido[2,3 : 2′,3′]-*p*-thiazine (V), 6-chloro-5′-methyl-6′-ethoxycarbonylpyrido[2,3 : 2′,3′]-*p*-thiazine (VI), and 6-chloro-5′,6′-diphenylpyrido[2,3 : 2′,3′]-*p*-thiazine (VII), respectively.

The stability of these 6-chloropyrido[2,3 : 2′,3′]-*p*-thiazines depends largely upon the position and variety of the substituents in the thiazine ring concerned.

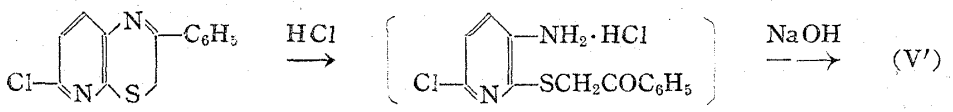
Kiprianov[4] recently reported the synthesis of 3-methylbenzo-*p*-thiazine by the interaction of chloroacetone and *o*-aminothiophenol in ether. However, one of the present authors and his collaborator failed to isolate 6-ethoxy-5′-methylpyrido[2,3:2′,3′]-*p*-thiazine because of its high unstability. We have now succeeded berely in obtaining (IV) under mild reaction conditions, by the treatment of (II) with bromoacetone by means of aqeuous potassium hydroxide at room temperature. (IV) was very susceptible to heat, undergoing vigorous decomposition when attempts were made to recrystallize it from a variety of solvents. The unstability of pyrido-*p*-thiazine possessing a methyl group at the neighbouring position to nitrogen atom in the thiazine ring, as is different in the case of benzo-*p*-thiazine, was also recognized in pyrido[3,4 : 3′,2′]-*p*-thiazine. When the present authors tried to synthesize 5′-substituted pyrido[3,4 : 3′,2′]-*p*-thiazine after Zincke's synthetic method[5] of benzo-*p*-thiazine, the reductive ring formation of (IX) to (X) occurred, though its yield was poor, whereas in the case of (VIII) employment of the same procedure resulted in the formation of a black resinous mass.



(VIII) $R=CH_2COCH_3$
(IX) $R=CH_2COC_6H_5$

(X)

6-Chloro-5′-phenylpyrido[2,3 : 2′,3′]-*p*-thiazine (V) was stable to alkali, and suffered no change even when boiled with 20% caustic soda, but it dissolved in concentrated hydrochloric acid to give a positive diazo reaction for primary arylamines, by which the hydrolysis as shown by the following formulae might be suggested.



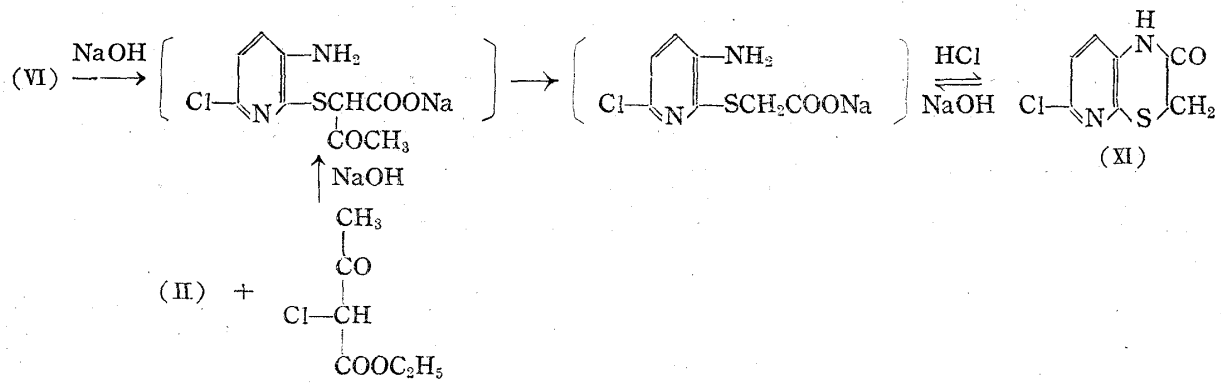
(V) m.p. 148~149°

m.p. 245°(decomp.)

Neutralization of the hydrochloric acid solution of (V) deposited crystals, which after recrystallization afforded (V′) as light yellow rhombics, m.p. 245°(decomp.), identical with the condensation product of (II) with phenacyl bromide in pyridine or ethanol. The fact that the conversion of (V) into (V′) also observed by heating in acetic anhydride or repeated recrystallization of the former suggested that they might be dimorphic. It seems, therefore, appropriate to distinguish the high melting (V′) from the low one by designating the initial letter " iso ", just as with 6-ethoxy-5′-phenylpyrido[2,3 : 2′,3′]-*p*-thiazine in the previous report.[1]

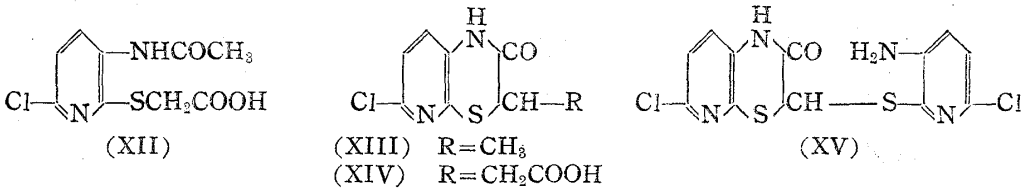
(VI) was indifferent to cold acids but sensitive to caustic alkali, and when heated with boiling 20% sodium hydroxide solution, ring cleavage took place to give a clear solution, from which (XI) was obtained after acidification with hydrochloric acid. Formation of (XI) may be supposed to proceed via sodium 3-amino-6-chloropyridylmercapto-(2)-acetoacetate → sodium 3-amino-6-chloropyridylmercapto-(2)-acetate, which often

4) A. I. Kiprianov : J. Gen. Chem.(U. S. S. R.), **21**, 156(1951)(C. A., **45**, 7574(1951)).
5) T. Zincke : Ann., **416**, 108(1918).



could be isolated as colorless needles exceedingly soluble in water. The same mechanism was also presented in the condensation reaction of (II) and ethyl α-chloroacetoacetate in the presence of excess alkali.

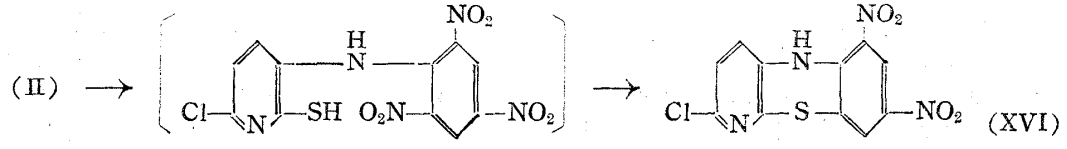
(II) readily condensed with appropriate α-halocarboxylic acids in the presence of sodium hydroxide to give 6-chloro-5′-oxo-5′,6′-dihydropyrido[2,3 : 2′,3′]-*p*-thiazine derivatives, the common property of which is that they dissolve in caustic alkali to undergo cleavage of the thiazine ring and recovered unchanged on adjusting pH to 4 with hydrochloric acid, hydrolysis of the lactam also being caused by excess acid.



Acetylation of (XI) with acetic anhydride brought about ring opening to give 3-acetamido-6-chloropyridylthio-(2)-acetic acid (XII).

(XIII) was obtained by the interaction of (II) and α-bromopropionyl bromide under the same conditions as employed in the foregoing paper.[1]

The preparation of bicyclic ketothiazine by fusing together α,β-unsaturated acid and *o*-aminothiophenol had been found by Mills and Whitworth,[6] and its extension to pyridine homologs, to the synthesis of 6-ethoxy-5′-oxo-6′-carboxymethyl-5′,6′-dihydropyrido[2,3 : 2′,3′]-*p*-thiazine, had been performed by the writer(T) and his collaborator. It is noteworthy to compare the foregoing successful result in employing 2-mercapto-3-amino-6-ethoxypyridine in place of (II) with the failure in the attempts to obtain (XIV) from (II) and maleic acid. For the preparation of (XIV) only the standard synthetic method of ketothiazines using bromosuccinic acid was found to be applicable.



The facile method for the preparation of dinitrophenothiazine by Misslin and Bau[7] was applied to that of 7,9-dinitro-3-chloro-2-azaphenothiazine (XVI), and the formation of (XVI) was supposed to proceed through pyridylpicrylamine, since Petrow and Rewald[8] isolated it as an intermediate and furthermore, the authors detected nitrite in the reaction mixture.

6) W. H. Mills, J. B. Whitworth : J. Chem. Soc., **1927**, 2738.
7) E. Misslin, A. Bau : Helv. Chim. Acta, **2**, 285(1919).
8) V. A. Petrow, E. L. Rewald : J. Chem. Soc., **1945**, 313.

Experimental*

3,3′-Diamino-6,6′-dichlorodipyridyl 2,2′-Disulfide (III)—A suspension of 0.5 g. of (II) in 15 cc. of EtOH was refluxed for 1 hr. Orange rhombics contaminated with light yellow needles deposited on cooling, which were collected and treated with 2% NaOH solution to remove the phenolic starting material (II). Orange rhombics remaining undissolved were recrystallized from AcOEt and had m.p. 210°. *Anal.* Calcd. for $C_{10}H_8N_4Cl_2S_2$: C, 37.62; H, 2.51. Found: C, 37.84; H, 2.69. (III) was occasionally formed as a by-product in the subsequent experiments starting from (II) and, in each case, the isolation of (III) was carried out by applying either fractional recrystallization or treatment with alkali.

6-Chloro-5′-methylpyrido[2,3 : 2′,3′]-*p*-thiazine (IV)—A solution of 0.4 g. of bromoacetone in 2 cc. MeOH was gradually poured into a solution of 0.33 g. of (II) in 6 cc. of 20% aq. KOH solution, when a crystalline substance separated. After standing at room temperature until no further precipitation occured, the deposit was filtered, washed with dil. MeOH, and purified by reprecipitating from MeOH–H_2O to colorless plates, m.p. 130~131°. Yield, 0.3 g. This was soluble in MeOH, ether, and AcOEt and decomposed to resin when heat was applied. *Anal.* Calcd. for $C_8H_7N_2ClS$: C, 48.87; H, 4.03. Found: C, 48.46; H, 3.95.

6-Chloro-5′-phenylpyrido[2,3 : 2′,3′]-*p*-thiazine (V)—To a solution of 0.5 g. of (II) in 10 cc. of 2% methanolic KOH solution was added 0.65 g. of phenacyl bromide, whereby the reaction proceeded under distinct color change from colorless to blood red. After 30 mins.' standing, the deposited crystalline substance was collected and recrystallized from MeOH to light yellow needles, m.p. 148~149°. Yield, 0.5 g. *Anal.* Calcd. for $C_{13}H_9N_2ClS$: C, 59.88; H, 3.45; N, 10.50. Found: C, 59.54; H, 3.71, N, 10.61.

Iso-6-chloro-5′-phenylpyrido[2,3 : 2′,3′]-*p*-thiazine (V′)—A stirred mixture of 0.5 g. of (II) and 0.65 g. of phenacyl bromide in 10 cc. EtOH was refluxed for 2 hrs. On cooling, crystals which separated out were recrystallized from AcOEt to light yellow rhombics, m.p. 245°(decomp.), sparingly soluble in AcOEt and MeOH. Yield, 0.1 g. *Anal.* Calcd. for $C_{13}H_9N_2ClS$: C, 59.88; H, 3.45. Found: C, 59.76; H, 3.48. (V′) was also obtained in the following cases: i) By the condensation of (II) with phenacyl bromide in dry pyridine. ii) By neutralization of HCl solution of (V) with NaOH. iii) By either heating in Ac_2O or repeated recrystallization of (V).

6-Chloro-5′-methyl-6′-ethoxycarbonylpyrido[2,3 : 2′,3′]-*p*-thiazine (VI)—0.5 g. of (II) was condensed with 0.5 cc. of ethyl α-chloroacetoacetate in 10 cc. of boiling EtOH for about half an hour. The red solution obtained was then poured into 20 cc. of water, giving orange red crystals, which were recrystallized from MeOH with charcoal to fine orange red needles, m.p. 203~204°(decomp.), soluble in hot MeOH and insoluble in benzene, ether, AcOEt, and cold MeOH. Yield, 0.2 g. *Anal.* Calcd. for $C_{11}H_{11}O_2N_2ClS$: C, 48.65; H, 4.06. Found: C, 48.62; H, 3.81.

6-Chloro-5′,6′-diphenylpyrido[2,3 : 2′,3′]-*p*-thiazine (VII)—0.7 g. of chlorodesoxybenzoin in 5 cc. of MeOH was added exothermally to a solution of 0.5 g. of (II) in 2% of KOH solution and the resulting red reaction mixture was heated on a water bath until yellow coloration was attained. After standing for 24 hrs., the solution was evaporated to dryness in a vacuum and the resinous residue extracted with ether to separate into two different parts; the ethereal part, on recrystallization from MeOH, yielded (VII) crystallizing in light yellow prisms, m.p. 132~133°, and the other which remained undissolved in the same solvent represented an unidentified product forming colorless plates, m.p. 201°(decomp.). Yield, 0.1 g. *Anal.* Calcd. for $C_{19}H_{13}N_2ClS$: C, 67.76; H, 3.86. Found: C, 67.30; H, 3.86.

3-Nitro-4-acetonylmercaptopyridine (VIII)—To a solution of 0.5 g. of 3-nitro-4-mercaptopyridine[9] in MeOH containing 0.3 g. of NaOH was gradually added 0.4 g. of bromoacetone with stirring, after which the reacting solution was set aside at room temperature for 1 hr. Removal of the solvent *in vacuo* gave a yellow mass, which was thoroughly washed with water and recrystallized from MeOH to light yellow plates melting at 103~104°. Yield, 0.4 g. *Anal.* Calcd. for $C_8H_8C_3N_2S$: N, 13.21. Found: N, 13.02.

3-Nitro-4-phenacylmercaptopyridine (IX)—0.3 g. of phenacyl bromide in a few cc. of MeOH was added into a solution of 0.5 g. of 3-nitro-4-mercaptopyridine. Crystals began to separate out immediately. Recrystallization was effected from AcOEt to light yellow plates, m.p. 184°. Yield, 0.5 g. *Anal.* Calcd. for $C_{13}H_{10}O_3N_2S$: N, 10.21. Found: N, 9.98.

5′-Phenylpyrido[3,4 : 3′,2′]-*p*-thiazine (X)—To a solution of 2 g. of stannous chloride dihydrate in 10 cc. of glacial AcOH saturated with dry HCl was added 0.5 g. of (IX) with vigorous stirring. After 1 hr.'s stirring at room temperature the deposited tin complex was decomposed by 20% NaOH and extracted with AcOEt and dried over anhydrous Na_2SO_4. Evaporation of the solvent left a resinous mass, which by recrystallization from MeOH, formed light yellow prisms, m.p. 144~145°. *Anal.* Calcd.

* All melting points are uncorrected.

9) T. Takahashi, K. Ueda, T. Ichimoto: This Bulletin, **2**, 199(1954).

for $C_{13}H_{10}N_2S$: C, 69.02; H, 4.42. Found: C, 68.48; H, 4.01.

6-Chloro-5'-oxo-5',6'-dihydropyrido[2,3 : 2',3']-*p*-thiazine (XI)—i) To a solution of 1 g. of (II) in 10 cc. of 10% KOH solution was added 0.6 g. of monochloroacetic acid. The mixture was heated at 80° for 1 hr., cooled, filtered, and acidified to pH 3~4 by adding conc. HCl. The light brown precipitate was collected and recrystallized from MeOH to colorless plates, m.p. 249~250°(decomp.). Yield, 0.5 g. *Anal.* Calcd. for $C_7H_5ON_2ClS$: C, 41.88; H, 2.44; N, 14.00. Found: C, 42.11; H, 2.65; N, 14.29. ii) 0.3 g. of ethyl α-chloroacetoacetate in 2 cc. of MeOH was gradually stirred into a solution of 0.33 g. of (II) in 5 cc. of 10% KOH solution, and the mixture allowed to stand at room temperature, depositing the potassium salt of an intermediate as colorless needles. Acidification of the diluted reaction mixture precipitated crude (XI), which was recrystallized from EtOH to form the same crystals as mentioned above. iii) (VI) was heated with 30% NaOH at 130~135° for 1 hr. The clear solution obtained was cooled, diluted with water, filtered, and rendered acidic by HCl, separating light brown precipitates from which after repeated recrystallization from EtOH colorless plates melting at 249° were obtained.

(XI) is sparingly soluble in organic solvents, soluble in caustic alkali and recoverable unchanged by neutralization with HCl.

3-Acetamido-6-chloropyridylmercapto-(2)-acetic Acid (XII)—0.1 g. of (XI) was treated with 4~5 cc. of Ac_2O in the usual manner. The acetate was recrystallized from MeOH to light red plates of m.p. 250~251°(decomp.). Yield, 0.08 g. *Anal.* Calcd. for $C_9H_9O_3N_2ClS$: C, 41.47; H, 3.46. Found: C, 41.40; H, 3.52.

6-Chloro-5'-oxo-6'-methyl-5',6'-dihydropyrido[2,3 : 2',3']-*p*-thiazine (XIII)—To a solution of 0.3 g. of (II) in 4 cc. of dry pyridine was added exothermally 0.41 g. of α-bromopropionyl bromide, after which the mixture was set aside for 3 hrs. and diluted with four-fold quantities of water, depositing colorless needles. Recrystallization was effected from MeOH to colorless needles, m.p. 230°(decomp.). Yield, 0.2 g. *Anal.* Calcd. for $C_8H_7ON_2ClS$: C, 44.75; H, 3.35. Found: C, 44.65; H, 3.35.

6-Chloro-5'-oxo-6'-carboxymethyl-5',6'-dihydropyrido[2,3 : 2',3']-*p*-thiazine (XIV)—A mixture of 0.5 g. of (II) and 0.62 g. of bromosuccinic acid in 10 cc. of 7% KOH was heated on a boiling water bath for 1 hour, cooled, filtered, and acidified with HCl. The white precipitate which separated out was collected and recrystallized from EtOH to colorless needles melting at 233~234°. Yield, 0.3 g. *Anal.* Calcd. for $C_9H_7O_3N_2ClS$: C, 41.78; H, 2.71. Found: C, 41.82; H, 2.92.

6-Chloro-5'-oxo-6'-[3''-amino-6''-chloropyridyl-(2'')]mercapto-5',6'-dihydropyrido[2,3 : 2',3']-*p*-thiazine (XV)—To a solution of 0.3 g. of (II) in MeOH containing 0.1 g. of KOH was added 0.2 g. of ethyl dichloroacetate, and the mixture heated at 65° for 1 hr., cooled, neutralized exactly to pH 5 by adding HCl, and set aside. The light yellow precipitate thus obtained was recrystallized from MeOH to light yellow crystals melting at 230~231°(decomp.). Yield, 0.2 g. *Anal.* Calcd. for $C_{12}H_8ON_4Cl_2S$: C, 40.11; H, 2.25. Found: C, 40.27; H, 2.49.

7,9-Dinitro-3-chloro-2-azaphenothiazine (XVI)—A suspension of 0.4 g. of (II) and 0.6 g. of trinitroanisole in 20 cc. of EtOH was refluxed for 30 mins. Then 0.1 g. of KOH in water was added dropwise to the brown solution and heating was continued for a further 30 mins. until permanent purple coloration was obtained. The filtered solution while hot deposited (XVI) which was recrystallized from AcOEt with charcoal to black needles, m.p. 260~261°(decomp.). Yield, 0.25 g. *Anal.* Calcd. for $C_{11}H_5O_4N_4ClS$: C, 40.67; H, 1.54. Found: C, 40.60; H, 1.80. The filtrate of the reaction mixture was evaporated to dryness; an aqueous extract of the residue gave a positive nitrite test with various reagents.

Summary

1) Synthesis of derivatives of 6-chloropyrido[2,3 : 2',3']-*p*-thiazine, 5'-oxo-5',6'-dihydropyrido[2,3 : 2',3']-*p*-thiazine, pyrido[3,4 : 3',2']-*p*-thiazine, and 2-azaphenothiazine was described.

2) Some of their chemical properties, especially their behavior to acids and alkalis, were investigated.

3) The reaction using 2-mercapto-3-amino-6-chloropyridine as one of the starting materials often afforded the by-product of orange rhombics, m.p. 210°, which was proved to be 3,3'-diamino-6,6'-dichlorodipyridyl 2,2'-disulfide.

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