87. Torizo Takahashi and Eiichi Yoshii: Sulfur-containing Pyridine Derivatives. XLII.* Synthesis of Pyrido[2,3:2′,3′]-*p*-thiazine. (1).

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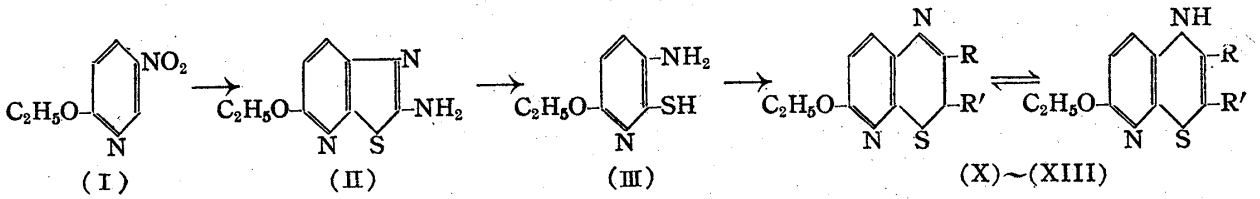
In one of the preceding papers,[1] Takahashi and Yamamoto reported the synthesis of pyridothiazoles by the thiocyanation of aminopyridines possessing electron-releasing substituent in the α-position of pyridine ring, viz., 2,5-diaminopyridine, 2,6-diaminopyridine, 2-alkoxy-5-aminopyridine, etc., and their conversion into the *o*-aminomercaptopyridine derivatives.

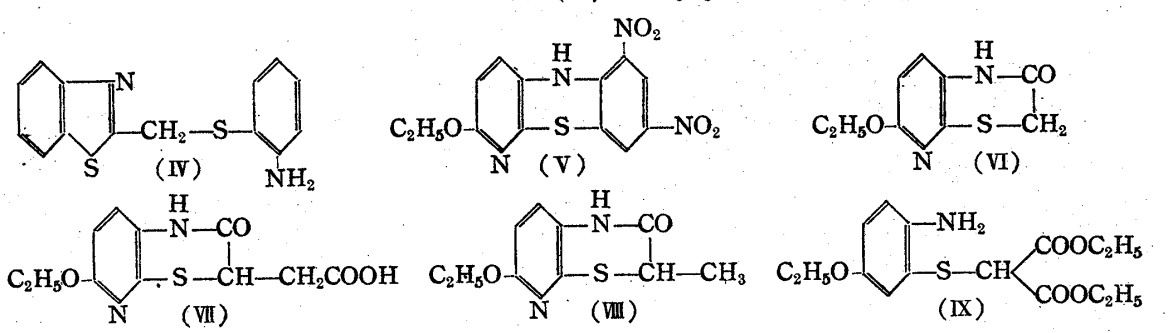
The present paper describes the synthesis of a new condensed pyrido-*p*-thiazine ring and some of its chemical properties with reference to the foregoing papers.

The key intermediate in the present work was (Ⅲ),[2] the preparation of which was effected by the alkaline hydrolysis of 2-amino-6-ethoxypyrido[2,3 : 5′,4′]thiazole (Ⅱ), obtained by the reduction of 2-ethoxy-5-nitropyridine (Ⅰ)[3] with stannous chloride, followed by ring formation with potassium thiocyanate and bromine in acetic acid.



(Ⅰ) (Ⅱ) (Ⅲ) (X)～(XIII)

(X) R=NH_2, R′=H; (XI) R=CH_3, R′=$COOC_2H_5$
(XII) R=C_6H_5, R′=H; (XIII) R=C_6H_5, R′=C_6H_5



(Ⅳ) (Ⅴ) (Ⅵ) (Ⅶ) (Ⅷ) (Ⅸ)

The facile synthesis of dinitrophenoxazines from picryl chloride and *o*-aminophenol in the presence of alkali was discovered by Turpin[4] and Kehrmann.[5] Subsequently, the reaction was applied to the pyridine homologs by Petrow and Rewald.[6] Attempts were made to extend the reaction to the readily available 2-mercapto-3-amino-6-ethoxypyridine (Ⅲ). Numerous experiments were carried out under various conditions, but the product, which was an unknown, highly colored needles, m.p. 209°, dissolved in alkali with the production of intense purple color. Similar results had been observed with the analogous 3-amino-4-hydroxypyridine and 3-amino-4-hydroxyquinaldine by foreign wokers.[6,7] Petrow and Rewald explained this result to compare with the reaction on dinitrophenylpy-

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1) J. Pharm. Soc. Japan, **71**, 622, 916, 920, 1436(1951).
2) Y. Yamamoto: *Ibid.*, **71**, 919(1951).
3) H. L. Friedmann, *et al.*: J. Am. Chem. Soc., **69**, 1204(1947).
4) G. S. Turpin: J. Chem. Soc., **59**, 714(1891).
5) F. Kehrmann: Ber., **32**, 2603(1899).
6) V. A. Petrow, E. L. Rewald: J. Chem. Soc., **1945**, 313, 592.
7) M. Conrad, L. Limpach: Ber., **20**, 950(1887).

ridinium chloride, the addition compound of chlorodinitrobenzene and pyridine, which undergoes conversion into the colored derivative of glutaconaldehyde on treatment with alkali. Successful result was ultimately obtained in preparing from (Ⅲ) an azaphenothiazine, 7,9-dinitro-3-ethoxy-2-azaphenothiazine (V), according to the modification of Misslin and Bau[8] who replaced picryl chloride with trinitroanisole.

Treatment of (Ⅲ) with monochloroacetic acid under the presence of two equivalents of potassium hydroxide, followed by acidification with hydrochloric acid, afforded 6-ethoxy-5′-oxo-5′,6′-dihydropyrido〔2,3 : 2′,3′〕-*p*-thiazine (Ⅵ). (Ⅵ) was also obtained by using either ethyl chloroacetate in pyridine or chloromalonic acid in place of monochloroacetic acid, or by the alkaline hydrolysis of diethyl 3-amino-6-ethoxypyridylmercapto-(2)-malonate (Ⅸ).

Several workers[9] have reported the addition reaction of thiols, and the preparation of bicyclic ketothiazines by fusing together *o*-aminothiophenol and α,β-unsaturated acid is the one used by Mills and Whitworth.[10] In the present series of experiments, condensation of (Ⅲ) with maleic or fumaric acid was investigated. This reaction, in case of the former, proceeded under mild reaction conditions, the condensation being completed by gentle warming of a fine mixture of both components. On the other hand, isomeric fumaric acid did not react even at about 150°, and above this point, (Ⅲ) underwent some decomposition. For the purpose of identifying this substance with 6-ethoxy-5′-oxo-6′-carboxymethyl-5′,6′-dihydropyrido〔2,3 : 2′,3′〕-*p*-thiazine (Ⅶ), advantage was taken of the standard synthetic method employing bromosuccinic acid.

It is generally known that the condensation of *o*-aminothiophenol with acid halides leads to the formation of 2-alkylbenzothiazoles. In case of the α-haloacid halides, the formation of either thiazole or ketothiazine ring would be expected. Unger and Graff[11] reported the formation of *o*-aminophenylthiomethylbenzothiazole (Ⅳ) as the condensation product of bromoacetyl bromide with two molecules of *o*-aminothiophenols. Warming (Ⅲ) with α-bromopropionyl bromide in dry pyridine furnished 6-ethoxy-6′-methyl-5′-oxo-5′,6′-dihydropyrido〔2,3 : 2′,3′〕-*p*-thiazine (Ⅷ) as colorless needles possessing the general properties of 5′-oxopyrido-*p*-thiazine.

5′-Amino derivative of 6-ethoxypyrido〔2,3 : 2′,3′〕-*p*-thiazine (X) was obtained by the reaction of (Ⅲ) with chloroacetonitrile by means of sodium ethoxide in absolute ethanol.

Condensation of (Ⅲ) with ethyl α-chloroacetoacetate, phenacyl bromide, and chlorodesoxybenzoin in aqueous pyridine or ethanol afforded 6-ethoxy-5′-methyl-6′-carbethoxypyrido〔2,3 : 2′,3′〕-*p*-thiazine (XI), 6-ethoxy-5′-phenylpyrido〔2,3 : 2′,3′〕-*p*-thiazine (XII), and 6-ethoxy-5′,6′-diphenylpyrido〔2,3 : 2′,3′〕-*p*-thiazine (XIII), respectively. For the satisfactory result pyridine was superior to any other solvents because of high yield and simple operation. The reaction between phenacyl bromide and (Ⅲ) became somewhat complex depending upon the reaction conditions employed as follows :

(i) In aq. pyridine at 75°, two crystalline substances were isolated in almost equal amounts : One, as yellow prisms, m.p. 125°, soluble in ether, and the other as colorless needles, m.p. 196.5°, insoluble in the same solvent.

(ii) Refluxing for 2 hrs. in alcohol afforded three different compounds. The main product, with a small amount of a mixture of m.p. 125° and 196.5°, both of which were found to be identical with the products obtained above, was yellow rhombs, m.p. 256°, insoluble in all organic solvents except hot nitrobenzene.

8) E. Misslin, A. Bau : Helv. Chim. Acta, **2**, 295(1919).
9) Bougaut, Chabrier : Compt, rend., **224**, 395(1947); C. D. Hurd, L. L. Gershbeim : J. Am. Chem. Soc., **69**, 2328(1947); L. N. Owen, H. M. B. Somade : J. Chem. Soc., **1947**, 1030.
10) W. H. Mills, J. V. Whitworth : J. Chem. Soc., **1927**, 2738.
11) O. Unger, G. Graff : Ber., **30**, 2389(1897).

(iii) One hour's reflux in ethanol with one equivalent portion of 2% sodium hydroxide resulted in the formation of a resinous mass, from which the above-mentioned crystals of m.p. 196.5° were separated.

In spite of the concordance with 6-ethoxy-5'-phenylpyrido[2,3 : 2',3']-*p*-thiazine (XII) in analytical results, the two compounds of m.p. 125° and m.p. 256° were quite different in properties. However, there are substantial reasons for supporting the view that they are dimorphic, because the former converts into the latter on boiling in acetic anhydride and the mixed fusion gives an intermediate melting point of the two. Therefore, the authors distinguished the high melting substance from the low one by giving the initial letter of "iso". Molecular weight determination of the substance of m.p. 196.5° by the Rast method gave a value of 450±15, suggesting that this was not a simple substance. Although its structure remained still unestablished, an attempt to convert it into the known compound was made. Treatment with boiling acetic anhydride furnished a resinous mass, from which two crystalline products were obtained by extraction with ethyl acetate followed by fractional recrystallization. One separated from the ethyl acetate-soluble portion and identified as iso-6-ethoxy-5'-phenylpyrido[2,3 : 2',3']-*p*-thiazine; the other, crystallizing in colorless needles, m.p. 117°, was still unidentified.

Stabiltiy of pyridothiazines above synthesized depends largely upon the position and variety of the substituents in the thiazine ring.

5'-Oxothiazine representable by (VI) is soluble in caustic alkali and recoverable unchanged by neutralizaton with hydrochloric acid. Attempt to chlorinate the enolizable intramolecular amide with phosphoryl chloride or phosphorus pentachloride was unsuccessful, only yielding a halogen-free purple pigment. Unger had also observed this result with 3-oxobenzo-*p*-thiazine.

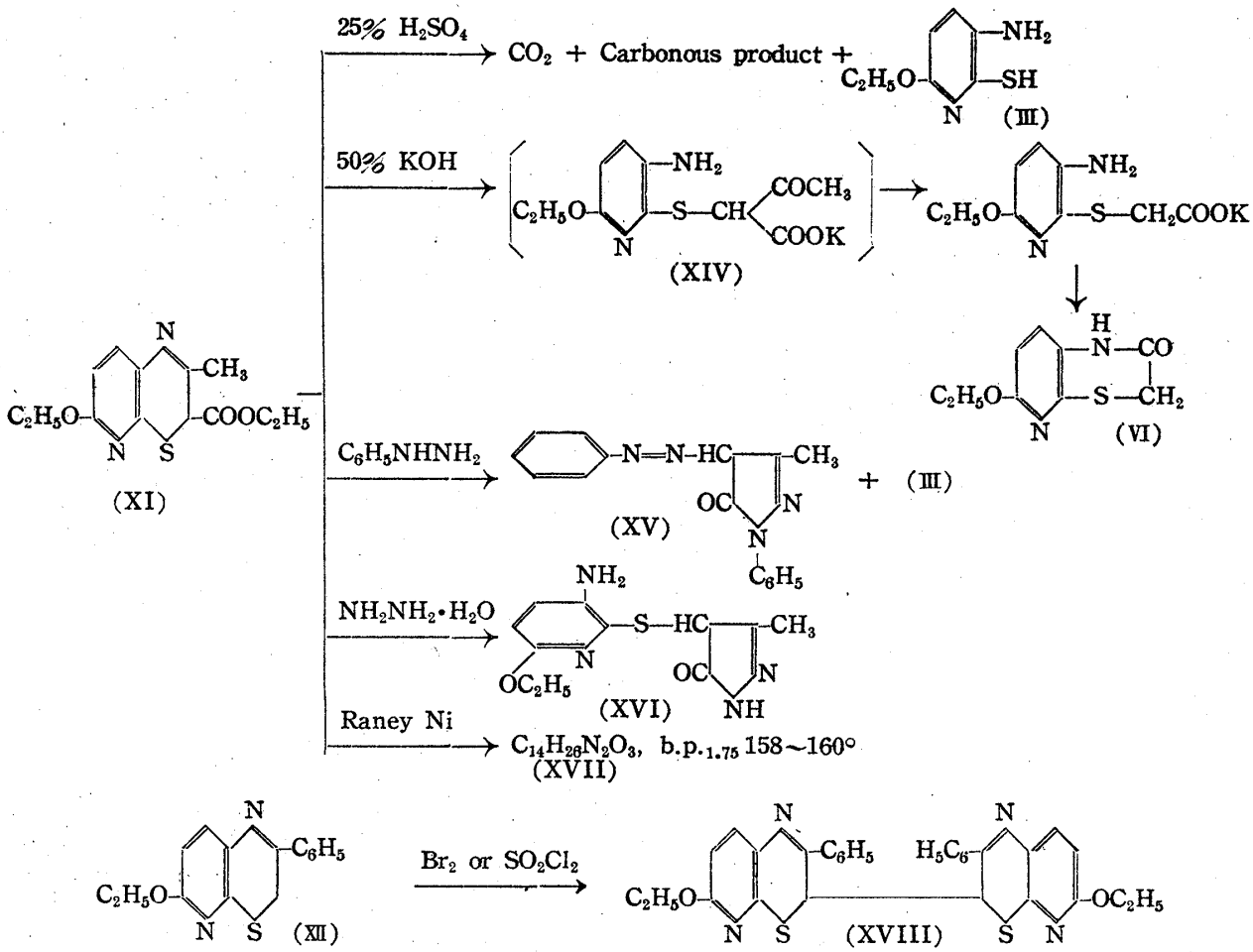
Kiprianov[12] recently reported the synthesis of 3-methylbenzo-*p*-thiazine by the interaction of chloroacetone and *o*-aminothiophenol in ether. 6-Ethoxy-5'-methylpyrido[2,3 : 2',3']-*p*-thiazine, however, was so unstable even in the form of hydrochloride that effort to isolate it in pure form was in vain.

On the other hand, (XI), (XII), and (XIII) were comparatively stable under dry conditions, but on standing for several weeks at a room temperature some change in color was observed.

The thiazine ring of (XI) was easily cleaved by treating with mineral acids, caustic alkali, and even with organic bases of strong basicity. On heating with 25% sulfuric acid at 100°, (XI) decomposed with vigorous evolution of carbon dioxide giving a dark viscous solution, from which after filtering off the carbonaceous product, followed by neutralization, the yellow (III) was obtained. Characterization of (III) was performed by leading it to the picrate and diacetate[1]. In case of employing 50% potassium hydroxide, ring cleavage occured between position 4 and 5 to give (VI) *via* potassium 3-amino-6-ethoxypyridylmercapto-(2)-acetoacetate (XIV), as shown in the following scheme. Similary, hydrazine hydrate formed 4-mercaptopyrazolone derivatives (XVI), the diazonium salt of which, on treatment with alkaline β-naphthol, yielded a blood-red dye. Phenylhydrazine afforded (III), and 1-phenyl-3-methyl-4-phenylazopyrazolone-(5) (XV),[13] identical in all respects with a specimen prepared by the condensation of ethyl α-chloroacetoacetate and phenylhydrazine, as described by Schoenbrodt[13]. When heated with Raney Nickel in ethanol solution, desulfurization occurred, giving an oil (XVII) of $b.p._{1.75}$ 158~160°. By analysis it was found to possess an empirical formula of $C_{14}H_{26}O_3N_2$, and it formed a stable picrate, $C_{14}H_{26}O_3N_2 \cdot C_6H_3O_7N_3$; its structure is not known.

6-Ethoxy-5'-phenylpyrido[2,3 : 2',3']-*p*-thiazine (XII) is indifferent to acids and alkalis,

12) A. I. Kiprianov : J. Gen. Chem. (U. S. S. R.), **21**, 156(1951) (C. A., 7574(1951)).
13) R. Schoenbrodt : Ann., **253**, 192(1889).



but sensitive to oxidizing agents due to the active methylene at 6-position. Bromine or sulfuryl chloride acted as oxidizing agent to give 6′:6′-bis(6-ethoxy-5′-phenylpyrido[2,3:2′,3′]-*p*-thiazine) (XVIII).

Experimental[14]

2-Mercapto-3-amino-6-ethoxypyridine (III)—45 g. of 2-ethoxy-5-nitropyridine was added in small portions to a solution of 225 g. of $SnCl_2 \cdot 2H_2O$ in 450 cc. of 35% HCl with efficient stirring over a period of 20 mins., when the reduction proceeded with considerable evolution of heat. Stirring was continued at a room temperature for further 1.5 hrs., after which the reaction mixture was allowed to stand overnight. Evaporation of HCl *in vacuo* left a white residue, which, after alkalization with 30% aq. NaOH under careful cooling, followed by extraction with 5 successive portions of 100 cc. of ether, gave 37 g. of the crude 2-ethoxy-5-aminopyridine. To a well-stirred solution of this aminopyridine and 100 g. of KSCN in 500 cc. of 95% AcOH, cooled in ice and salt, was added dropwise a solution of 13.6 cc. Br_2 in 30 cc. AcOH, the temperature being kept below −4° throughout the addition and for an additional 30 mins. After stirring for 3 hrs. at a room temperature, the orange suspension was set aside overnight, filtered with suction, and poured into 1500 cc. of water. A small amount of amorphous precipitate was again filtered off and the filtrate was neutralized with about 100 g. Na_2CO_3; complete neutralization of AcOH was not required because of the weak basicity of the pyridothiazole obtained. The quantitatively precipitated 2-aminopyrido[2,3 : 5′,4′]thiazole (II) was recrystallized from MeOH with charcoal. One hr.'s boiling of 5 g. of (II) in 50 cc. of 20% aq. NaOH with 1 g. of arsenous acid, after acidification of the resulting clear solution by AcOH, yielded (III) almost quantitatively. Attempts to isolate it in crystalline form failed, and the crude (III) had no distinct melting nor decomposition point. An EtOH solution of (III), on treatment with a satd. solution of picric acid, gave a crystalline picrate, m.p. 151°(decomp.). *Anal.* Calcd. for $C_7N_{10}ON_2S \cdot C_6H_3O_7N_3$: C, 39.20; H, 3.26. Found : C, 39.34; H, 3.31. Treatment of (III) with Ac_2O on a water bath gave a diacetate as color-

14) All melting points are uncorrected.

less needles, m.p. 196~198°[1] after recrystallization from MeOH.

7,9-Dinitro-3-ethoxy-2-azaphenothiazine (V)—A mixture of (III) and 0.58 g. of trinitroanisole was refluxed for 1 hr. in 15 cc. MeOH, aq. NaOH was gradually added to the boiling blood-red solution until a permanent purple color was obtained, and the mixture was filtered while hot. The black needles which precipitated out were recrystallized from AcOEt with charcoal. Yield, 0.21 g., m.p. 212°. *Anal.* Calcd. for $C_{13}H_{10}O_5N_4S$: C, 46.70; H, 2.99. Found: C, 46.52; H, 3.20.

6-Ethoxy-5'-oxo-5',6'-dihydropyrido[2,3:2',3']-*p*-thiazine (VI)—(i) 0.5 g. of (III) was dissolved in 10 cc. of 4% aq. KOH and 0.3 g. of monochloroacetic acid in 5 cc. of water added. The mixture was warmed on a water bath at 80° for 45 mins., filtered on cooling, and neutralized by conc. HCl. The white precipitate obtained was collected and recrystallized from EtOH to colorless needles, m.p. 226°. Yield, 0.35 g. *Anal.* Calcd. for $C_9H_{10}O_2N_2S$: C, 51.43; H, 4.76; N, 13.33. Found: C, 51.65; H, 4.76; N, 13.29.

(ii) A mixture of 0.5 g. of (III), 3 cc. pyridine, 1.5 cc. EtOH, and 1.5 cc. water was warmed with 0.36 g. of ethyl chloroacetate at 80° for 2 hrs. with occasional shaking. After this period 10 cc. of water was added, cooled, and the crude (VI) thereby precipitated out was filtered. The recrystallization from EtOH gave 0.37 g. of colorless needles, m.p. 226°.

6-Ethoxy-5'-oxo-6'-carboxymethyl-5',6'-dihydropyrido[2,3:2',3']-*p*-thiazine (VII)—(i) A mixture of 0.5 g. of finely powdered (III) and 0.35 g. of maleic acid was heated at 105~110° for about 10 mins. The reaction proceeded with evolution of water and the whole soon solidified to a hard mass. The product was recrystallized from dilute EtOH, from which it separated in colorless needles, m.p. 198°. Yield, 0.6 g. *Anal.* Calcd. for $C_{11}H_{12}O_4N_2S$: C, 49.25; H, 4.47. Found: C, 49.31; H, 4.47.

(ii) A solution of 0.5 g. of (III) in a mixture of 10 cc. of water and 0.51 g. KOH was heated on a boiling water bath for 2 hrs. with 0.6 g. of bromosuccinic acid in 7 cc. of water after which the reaction mixture was cooled, filtered, and acidified with HCl. The white precipitate which separated out was collected and recrystallized from dil. EtOH to colorless needles, m.p. 197~198°, undepressed on admixture with the above compound.

6-Ethoxy-6'-methyl-5'-oxo-5',6'-dihydropyrido[2,3:2',3']-*p*-thiazine (VIII)—To a solution of 0.57 g. of (III) in 10 cc. of dry pyridine was added gradually 0.7 g. of α-bromopropionyl bromide under cooling. After standing for 40 mins., the reaction mixture was kept on a water bath for 30 mins. at 70°, diluted with 4 volumes of water, depositing colorless needles. Recrystallization was effected from MeOH to colorless needles, m.p. 166~167.5°. The analytical sample was dried at 50° *in vacuo* over P_2O_5. *Anal.* Calcd. for $C_{10}H_{12}O_2S$: N, 12.50. Found: N, 12.37.

Diethyl 3-Amino-6-ethoxypyridylmercapto-(2) Malonate (IX)—To a solution of 0.4 g. of (III) in 3 cc. pyridine, 1 cc. water, and 1 cc. EtOH was added 0.46 g. of diethyl chloromalonate. After 3 hrs.' standing at a room temperature, the resulting yellow solution was warmed on a water bath at 75° for 40 mins., cooled, and diluted with water, depositing a brown oil. The solidified mass was filtered with suction, washed with water, and after decolorization with charcoal recrystallized from aq. EtOH to colorless needles, m.p. 165°. Yield, 0.32 g. *Anal.* Calcd. for $C_{14}H_{20}O_5N_2S$: C, 51.21; H, 6.09. Found: C, 51.05; H, 6.25. The hydrolysis of the ester was effected by refluxing for 1hr. in a equimol. quantity of ethanolic KOH, and yielded (VI) on acidification with HCl.

6-Ethoxy-5'-amino-pyrido[2,3:2',3']-*p*-thiazine (X)—1 g. of (III), dissolved in 16 cc. of an ethanolic EtONa containing 0.26 g. of metallic Na, and 0.5 g. of chloroacetonitrile, were refluxed gently for 1.5 hrs. After removal of the solvent the residue was taken up in ether, washed with water, and the ether extract was dried over anhyd. K_2CO_3. The residue remaining after removing the ether was recrystallized from EtOH to colorless plates, m.p. 198°(decomp.). *Anal.* Calcd. for $C_9H_{11}ON_3S$: N, 20.09. Found: N, 19.61.

6-Ethoxy-5'-methyl-6'-carbethoxypyrido[2,3:2',3']-*p*-thiazine (XI)—(i) To a solution of 0.3 g. of (III) in a mixture of 1 cc. of water and 2 cc. of pyridine was added 0.3 g. of ethyl α-chloroacetoacetate using necessary amount of MeOH for complete solution. After 1.5 hrs.' standing at a room temperature, the content was warmed at 65° for 30 mins., then cooled, and diluted with water. The precipitated orange solid, when recrystallized from EtOH, gave (XI), as orange crystals of m.p. 157°. *Anal.* Calcd. for $C_{13}H_{16}O_3N_2S$: C, 55.71; H, 5.71. Found: C, 55.71; H, 5.84.

(ii) The crude (III) was condensed with 0.5 g. of ethyl α-chloroacetoacetate in 10 cc. of boiling EtOH for about 2 hrs. The red solution obtained was poured into 30 cc. of water and gave orange deposit, which was made alkaline with 25% aq. NH_4OH, filtered, and recrystallized from EtOH to orange needles, m.p. 156~157°.

Action of 50% KOH on (XI)—0.5 g. of (XI) was heated with 15 cc. of 50% KOH in an oil bath at 130~140°. The reaction proceeded with distinct color change from white to dark. After 1 hr.'s refluxing, the reaction mixture was treated with the minimum quantity of water to dissolve any floating substances, filtered with charcoal, cooled, and rendered acid with HCl. The grey precipitate

thus obtained was recrystallized 3 times from EtOH with charcoal, giving 6-ethoxy-5'-oxo-5',6'-dihydropyrido[2,3:2',3']-*p*-thiazine (VI) as colorless needles of m.p. 226°. Admixture with an authentic specimen, m.p. 226°, showed no depression.

Action of Phenylhydrazine on (XI)—A solution of 0.3 g. of (XI) in 10 cc. EtOH was heated with excess phenylhydrazine on a water bath. After 4 hrs.' refluxing, an orange solid which precipitated on cooling was filtered, washed with cold EtOH, and recrystallized from the same solvent to 4-phenylazo-1-phenyl-3-methylpyrazolone-(5)(XV), as red needles of m.p. 155°. This compound coincided with an authentic sample prepared by the reaction of phenylhydrazine on ethyl *α*-chloroacetoacetate after Schoenbrodt.[13] *Anal.* Calcd. for $C_{16}H_{14}ON_4$: C, 69.06; H, 5.03; N, 20.14. Found: C, 69.34; H, 5.25; N, 20.33. The filtrate was evaporated to dryness *in vacuo*, treated with ether, and the resulting precipitate was dissolved in aq. NaOH, and reprecipitated by AcOH to a yellow mass. The dried substance, after being treated with 3 cc. Ac_2O for 15 mins. on a boiling water bath, gave colorless 2-acetylmercapto-3-acetamino-6-ethoxypyridine, m.p. 196~198°, from MeOH. This was also characterized as the picrate, m.p. 151°(decomp.).

Ring Cleavage by H_2SO_4—A solution of 0.3 g. of (XI) in 15 cc. of 25% H_2SO_4 was heated on a boiling water bath for 1 hr. The reaction proceeded with evolution of CO_2 to a dark viscous solution, which was cooled, and adjusted to pH 2 with 25% aq. NH_4OH. The carbonous product which precipitated was filtered off and the filtrate was made alkaline with a further amount of aq. NH_4OH. The depositing yellow product was purified by dissolving in aq. NaOH and reprecipitated by AcOH. 2-Mercapto-3-amino-6-ethoxypyridine (III) obtained was characterized as the diacetate, m.p. 196~198°, and the picrate, m.p. 151°(decomp.).

Action of Raney Nickel on (XI)—A solution of 2.5 g. of (XI) in 250 cc. EtOH was refluxed for 1.5 hrs. with about 25 g. of freshly prepared Raney Ni catalyst. After standing overnight, the colorless mixture was filtered and the catalyst washed with EtOH. The filtrate and washings were fractionated. There was obtained 1.2 g. of a colorless oil free from sulfur, $b.p._{1.75}$ 158~160°. *Anal.* Calcd. for $C_{14}H_{26}O_3N_2$: C, 62.22; H, 9.62; N, 10.37; mol. wt., 270. Found: C, 62.76; H, 9.45; N, 10.18; mol. wt. (Rast), 262.

An ethereal solution of this oil with an ethereal picric acid gave a picrate, m.p. 115°, from aq. EtOH. *Anal.* Calcd. for $C_{14}H_{26}O_3N_2 \cdot C_6H_3O_7N_3$: C, 48.09; H, 5.81. Found: C, 48.04; H, 5.02.

Action of Hydrazine Hydrate on (XI)—A mixture of 0.3 g. of (XI) and 2 cc. of 80% hydrazine hydrate was heated in 5 cc. EtOH under reflux for 2 hrs. The reaction mixture, which at first gave a red color, changing to colorless, was evaporated to dryness *in vacuo*, and treated with three 20-cc. portions of benzene to extract any soluble substances, yielding a white solid, m.p. 225~228°. Recrystallization from MeOH gave colorless needles of 3-methyl-4-(3'-amino-6'-ethoxypyridyl-(2')-mercapto)-pyrazolone-(5)(XVI), m.p. 226°(decomp.). The diazonium salt of this substance gave blood-red dye when treated with an alkaline solution of *β*-naphthol. *Anal.* Calcd. for $C_{11}H_{14}O_2N_4S$: C, 49.62; H, 5.26; N, 21.05. Found: C, 49.79; H, 5.36; N, 20.08.

6-Ethoxy-5',6'-diphenylpyrido[2,3:2',3']-*p*-thiazine (XIII)—To a warm solution of 0.30 g. of (III) in 3 cc. of pyridine and 1 cc. of water was added a solution of 0.44 g. of chlorodesoxybenzoin in 5 cc. EtOH, the mixture was heated for 40 mins. on a water bath, and then poured into water. After cooling with ice, a resinous solid separated out. Treatment of the solid with ether gave the pyrido-*p*-thiazine, which crystallized from EtOH-AcOEt to light yellow prisms, m.p. 131~132°. Yield, 0.12 g. *Anal.* Calcd. for $C_{21}H_{18}ON_2S$: C, 72.83; H, 5.20. Found: C, 73.04; H, 5.20.

6':6'-Bis(6-ethoxy-5'-phenylpyrido[2,3:2',3']-*p*-thiazine)(XVIII)—(i) 0.16 g. of SO_2Cl_2 was added in small portions to a solution of 0.32 g. of (XII) in 10 cc. of benzene at a room temperature. The reaction mixture soon became dark green and after subsequent warming on a water bath at 60~65° for 40 mins., deposited reddish brown needles. On evaporation of the solvent there was obtained a brown mass, which after washing thoroughly with MeOH produced a clear red color. Recrystallization from hot nitrobenzene gave red needles, m.p. 297°. Yield, 0.28 g. *Anal.* Calcd. for $C_{30}H_{26}O_2N_4S_2$: C, 66.91; H, 4.83; N, 10.41. Found: C, 66.58; H, 4.55; N, 10.17.

(ii) To a cooled solution of 0.2 g. of (XII) in 10 cc. of glacial AcOH was added 0.04 cc. of Br_2 with shaking, and the mixture was allowed to stand at room temperature for 0.5 hr. The brown solid which separated was filtered, washed with water, and recrystallized from nitrobenzene or dioxane, m.p. 297°. Yield, 0.10 g.

Reaction of Phenacyl Bromide and 2-Mercapto-3-amino-6-ethoxypyridine—The condensation of (III) with phenacyl bromide was carried out in the following solvents: (i) aq. pyridine, (ii) EtOH, (iii) ethanolic KOH. In each case different product was obtained as follows:

(i) To a solution of 0.25 g. of (III) in aq. pyridine consisting of 1.5 cc. pyridine and 1 cc. water was added all at once 0.30 g. of phenacyl bromide and heating was continued at 70° for 40 mins. After cooling, the crude material that separated out was collected and dried in air. Extraction with ether furnished two crystalline products, of which one was yellow prisms, m.p. 125°, soluble in ether, and the other, colorless needles, m.p. 196.5° insoluble in the same solvent; both were recrystal-

lized from EtOH. The analytical results showed that the former was 6-ethoxy-5′-phenylpyrido[2,3:2′,3′]-*p*-thiazine (XII). *Anal.* Calcd. for $C_{15}H_{14}ON_2S$: C, 66.66; H, 5.18; N, 10.37. Found: C, 66.33; H, 5.46; N, 10.50. On the other hand, the latter was identical with the product obtained in (iii).

(ii) On heating 0.5 g. of (III) and 0.59 g. of phenacyl bromide in 15 cc. EtOH on a water bath, a yellow crystalline product separated, which after 2 hrs.' refluxing was taken up while hot and dissolved in hot nitrobenzene. Iso-6-ethoxy-5′-phenylpyrido[2,3:2′,′3]-*p*-thiazine crystallized in yellow rhombs, m.p. 256°. *Anal.* Calcd. for $C_{15}H_{14}ON_2S$: C, 66.66; H, 5.18; N, 10.37. Found: C, 66.37; H, 5.04; N, 10.11. After evaporation of the mother liquor, the residue was separated into two parts by ether extraction. Both were found to be identical with that obtained in (i).

(iii) To a solution of 0.5 g. of (III) in 10 cc. of 2% ethanolic KOH was added 0.59 g. of phenacyl bromide in 7 cc. of EtOH, and the mixture was heated on a water bath under reflux for 1 hr. Evaporation of the solvent left a yellow resinous mass, which yielded colorless needles of m.p. 196.5° after repeated recrystallization from EtOH. Yield, 0.16 g.

Summary

(1) Synthesis of the derivatives of pyrido[2,3:2′3′]-*p*-thiazine, 5′-oxo-5′,6′-dihydropyrido[2,3:2′,3′]-*p*-thiazine, and 2-azaphenothiazine, starting from 2-mercapto-3-amino-6-ethoxypyridine, was studied.

(2) Some of their chemical properties were also investigated.

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88. Eiji Ochiai, Toshihiko Okamoto, Tsutomu Sugasawa, und Shin-ichiro Sakai: Aconitum-Alkaloide. V[1]. Über die Konstitution des Ignavins. (2).

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In Fortsetzung der Versuche zur Konstitutionsermittelung des Ignavins[2] haben wir nun die Selen-Dehydrierung des Anhydroignavinols[3] ausgeführt.

Anhydroignavinol, $C_{20}H_{25}O_4N$, wurde nämlich mit 4 fachen Mengen pulverisiertem Selen innig gemischt und auf 340° 3 Stunden lang erhitzt. Die abweichenden Gase wurden dabei mit 5%iger Salzsäure gewaschen, um den flüchtigen Aminteil zu fassen. Die Reaktionsmasse wurde nach dem Zerkleinern wiederholt mit Benzol digeriert und die gesamte Benzol-Lösung durch Behandlung mit je 5%iger Salzsäure und Natronlauge in den neutralen, den basischen und den säurigen Teil getrennt. In der Tabelle I wird das Resumé der Experimente gezeigt.

Tabelle I.

	Exp. 1 (mg)	Exp. 2 (mg)	gesamt (mg)
Anhydroignavinol	2000	1500	3500
neutraler Teil	220	157	377
basischer Teil	160	154	314
säuriger Teil	7	12	19
flücht. Amin (HCl-Sz.)	69	59	128
gesamt	456	382	838

Aus dem flüchtigen basischen Teil wurden nur Ammoniak papierchromatographisch nachgewiesen.

Der im ganzen 377 mg betragende neutrale Teil wurde mittels Alumina-Säule nach flüssiger Chromatographie gereinigt. Die zuerst durch Entwickeln mit Benzol erhaltene

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1) IV. Mitteilung: Dieses Bulletin, **1**, 152(1953).
2) Dieses Bulletin, **1**, 60(1953).
3) J. Pharm. Soc. Japan, **72**, 821(1952).