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77. **Kan-ichi Ueda**: Sulfur-containing Pyridine Derivatives. L.* Mechanism of Cleavage of Thiazole Ring of 2-Aminothiazolo[5,4-*b*]pyridines by Means of Aqueous Alkali.

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It was already found by Yamamoto[1] that when 2-aminothiazolo[5,4-*b*]pyridines were refluxed with aqueous caustic alkali, the cleavage of the thiazole ring was brought about with comparative ease to give 2-mercapto-3-aminopyridines although benzothiazoles in general undergo the ring opening with considerable difficulty. This cleavage, which is characteristic of 2-aminothiazolopyridines, affords a simple method for the preparation of 2-mercapto-3-aminopyridines, by which, attempts to synthesize not only a variety of 2-substituted thiazolopyridines, but also other sulfur-containing pyridine derivatives are now in progress. However, studies on the mechanism of the ring cleavage have not so far appeared in previous reports, and also, it has been pointed out that in the synthesis of sulfur-containing pyridine derivatives from the 2-mercapto-3-aminopyridines, satisfactory results could not necessarily be expected.

As shown in Part XXXVIII of this series,[2] on treatment of the 2-mercapto-3-aminopyridines with alkylating agent in alkaline medium, the following results were obtained. Methylation of 3-amino-6-chloro-2-mercaptopyridine (I) with methyl iodide or dimethyl sulfate did not give the expected S-methyl ether, only resulting in the formation of structurally unknown crystals, m.p. 286°(Substance I). In the methylation as well as ethylation of 3-amino-6-ethoxy-2-mercaptopyridine(II), structurally unknown crystals, m.p. 204°(Substance II), and crystals, m.p. 161°(Substance III), were obtained as by-products, besides the S-methyl and -ethyl ethers, respectively.

Later, Takahashi and his co-workers[3] reported that in the synthesis of pyrido-1,4-thiazines, when (II) was allowed to condense with phenacyl bromide in alkaline medium, somewhat complicated results followed, depending upon the condition employed, and that in the alkaline hydrolysis of 2-amino-5-chlorothiazolo[5,4-*b*]pyridine, the application of barium hydroxide as a hydrolysis agent rather than sodium hydroxide gave 3-amino-6-chloro-2-mercaptopyridine in the higher degree of purity.

The object of this investigation is to study what causes the formation of unknown substances and thereby clarify the mechanism of the cleavage of thiazole ring.

Elucidation of the Structurally Unknown Substances

As a result of later studies, some different data from those described in Part XXXVIII were obtained (cf. experimental section), viz. (1) shifting of their analytical data, (2) absence of Liebermann's reaction, and (3) variation of their melting points.

First, the infrared and ultraviolet absorption spectra (Figs. 1, 2, and 3) of the unknown Substance I, 3-amino-6-chloro-2-methylthiopyridine (III), and 3-acetamido-6-chloro-2-methylthiopyridine (IV) were measured. While the infrared srectrum of (III) has two absorptions originating from the amino group near 3 μ, that of Substance I exhibits four absorptions (2.88, 3.01, 3.07, and 3.15 μ) in that region in addition to the

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[1] Y. Yamamoto: J. Pharm. Soc. Japan, **71**, 916(1951).

[2] T. Takahashi, K. Ueda: *Ibid.*, **73**, 442(1953).

[3] T. Takahashi, E. Yoshii: This Bulletin, **2**, 382(1954); T. Takahashi, Y. Maki: *Ibid.*, **3**, 92(1955).

characteristic carbonyl absorption (6.03 μ), thus suggesting the existence of $-NHCONH_2$ group. On comparison of the ultraviolet spectra of Substance I and (IV), there are observed close similarity in the intensity and wave lengths of their absorption maxima, whereas those of (III) are different. The similarity is most satisfactory, giving further support to the presence of a carbonyl group suggested by infrared examination. Since its diazo reaction for aromatic primary amines was positive, an attempt to acetylate Substance I was made, with the result that two kinds of substances were isolated. One was identified as 3-acetamido-6-chloro-2-methylthiopyridine (IV) by admixture, and the other, as colorless needles, m.p. 209°, whose analyses corresponded to N'-acetyl-N-(6-chloro-2-methylthiopyridyl-(3))urea (V). This behavior is similar to that of phenylurea toward acetic acid, which was studied by Dickmann and Kämmerer.[4] From these facts and analytical values it is evident that Substance I must be 6-chloro-2-methylthiopyridyl-3-urea (VII), and further evidence was provided by its synthesis in a usual manner[5] from (I) obtainable by the reaction of 2-amino-5-chlorothiazolo-[5,4-*b*]pyridine with barium hydroxide.

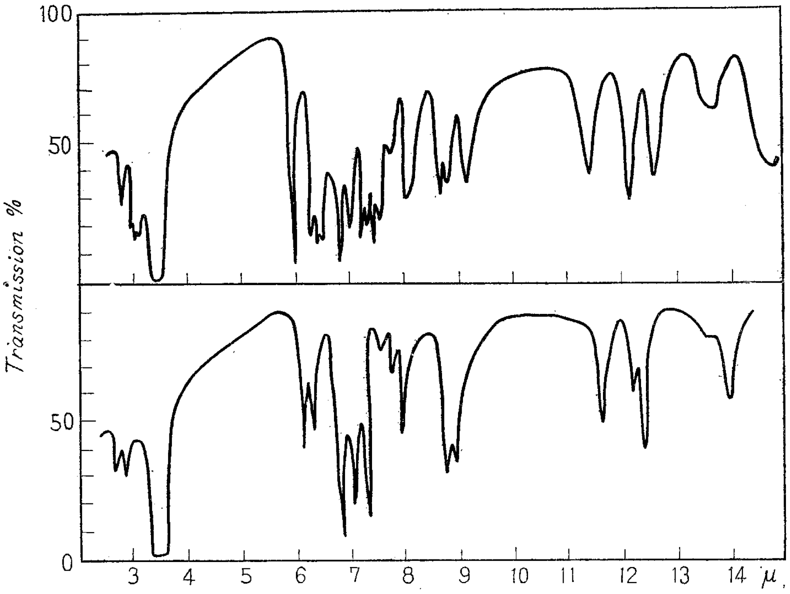

Fig. 1. (Ⅶ)

Fig. 2. (Ⅲ)

Infrared Spectra of 6-Chloro-2-methylthiopyridyl-3-urea (Ⅶ) and 3-Amino-6-chloro-2-methylthiopyridine (Ⅲ) (in Nujol)

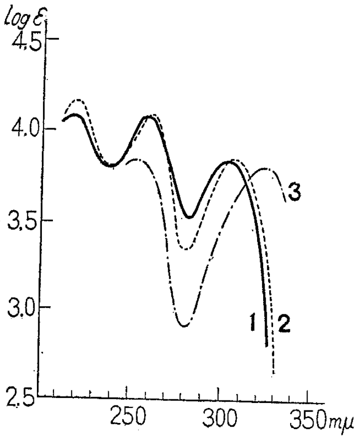

Fig. 3.

Ultraviolet Absorption Spectra (in abs. EtOH)

1. 3-Acetamido-6-chloro-2-methylthiopyridine
2. 6-Chloro-2-methylthiopyridyl-3-urea
3. 3-Amino-6-chloro-2-methylthiopyridine

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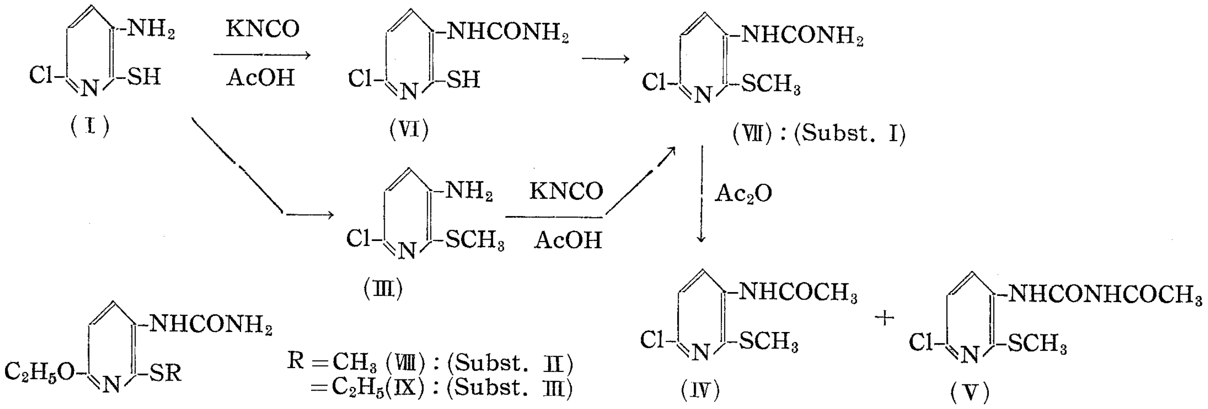
4) W. Dickmann, H. Kämmerer : Ber., **40**, 3742(1907).
5) Org. Syntheses, **31**, 8(1951).



When (I) was allowed to react with potassium cyanate in acetic acid, (VI) was obtained, subsequent methylation of which formed (VII). On the other hand, treatment of (III) with potassium cyanate also gave the same product (VII). Since the melting point of (VI) was indefinite and mixed melting point was not satisfactory, recourse was taken to infrared and ultraviolet spectra determination for the identity of Substance I and (VII).

Similarly, Substance II and III were determined as 6-ethoxy-2-methylthiopyridyl-3-urea (VIII) and 6-ethoxy-2-ethylthiopyridyl-3-urea, respectively, by their syntheses and comparing their ultraviolet spectra. The ultraviolet spectra of (VIII) and (IX) are given in Fig. 4.

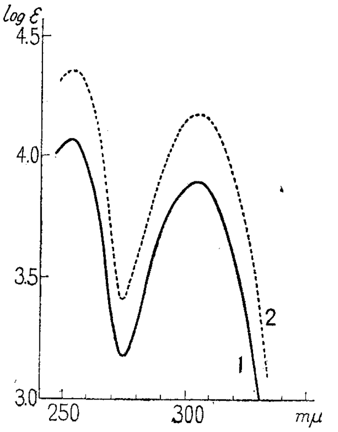


Fig. 4.

Ultraviolet Absorption spectra (in abs. EtOH)

1. 6-Ethoxy-2-methylthiopyridyl-3-urea
2. 6-Ethoxy-2-ethylthiopyridyl-3-urea

Consideration on the Formation of the Urea Product and Experimental Facts

As stated above, it should be considered that the formation of the urea product was not caused by methylation of 2-mercapto-3-aminopyridine but instead a substance like (VI) had been accompanied as an impurity in the starting material from the beginning. This supposition may be supported by the fact that the methylation of (VI) gave (VII) and that by prolonging time for cleavage reaction of the thiazolopyridine, subsequent alkylation of the resulting aminothiol caused a decrease of the formation of (VII) and an increase of that of (VIII). It is also evident from the fact that, as described in the experimental section, 6-ethoxy-2-mercaptopyridyl-3-urea (X) was isolated from the filtrate of (II) formed by 6.5 hrs.' reaction of 2-amino-5-ethoxythiazolo[5,4-*b*]pyridine. Therefore, it may well be considered that the mercaptopyridylurea was produced by the cleavage of the thiazole ring of the thiazolopyridine, and is an intermediate to the final product, 2-mercapto-3-aminopyridine.

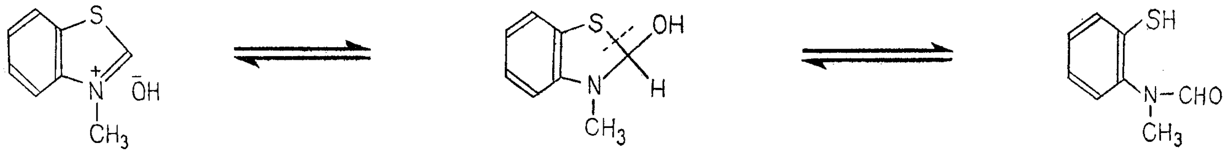
According to previous reports,[1,3] the cleavage of 2-amino-5-chlorothiazolo[5,4-*b*]pyridine required one hour in the use of sodium hydroxide and six hours in that of barium hydroxide. However, when 2-amino-5-chlorothiazolo[5,4-*b*]pyridine was refluxed with aqueous sodium hydroxide for 7 hrs. (I) was obtained in the higher degree of purity, which may be understood easily from the fact that on subsequent methylation it accompanied none of the by-products. Also, in the condensation of (II), obtainable after 10 hrs.' cleavage reaction of 2-amino-5-ethoxythiazolo[5,4-*b*]pyridine, with phenacyl bromide, the expected 6-ethoxy-2-phenylpyrido[2,3-*b*]-1,4-thiazine was obtained in a good yield, without formation of the unknown substance of m.p. 196°.

From these facts, it may be concluded that because of short reaction time, the cleavage reaction could not be completed so that the contamination of an intermediate brought about unsatisfactory results mentioned before.

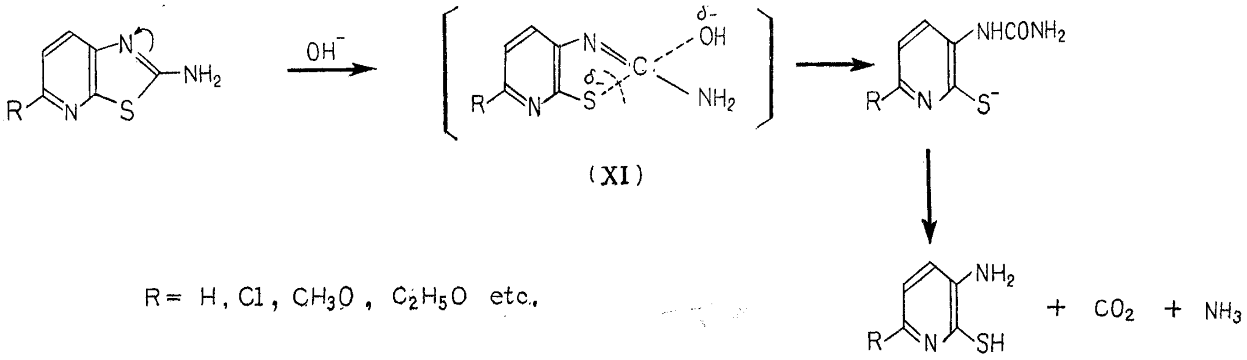
Mechanism of Cleavage of the Thiazole Ring of 2-Aminothiazolo[5, 4-*b*]pyridines

The 6 hours' hydrolysis of (VI) formed only the product giving (III) on methylation, whereas one hour's hydrolysis yielded two substances, (III) and (VII), after methylation. The ratio of their yields almost agreed with that of (III) and (VII) obtained by one hour's reaction of 2-amino-5-chlorothiazolo[5,4-*b*]pyridine with sodium hydroxide solution followed by methylation with dimethyl sulfate. Also, in the cases of (VI) and the thiazolopyridine, their reacticn accompanied the evolution of ammonia, which became remarkable within 10 mins. These facts seem to indicate clearly that cleavage of the thiazolopyridine proceeds in accordance with the following route, viz. aminothiazolopyridine→mercaptopyridylurea→mercaptoaminopyridine, and that the evolution of ammonia points towards the conversion of urea into the mercaptoaminopyridine and since it takes many hours for the completion of the hydrolysis, mercaptopyridylurea is resistant to this hydrolysis.

Among the literatures⁽⁶⁾ regarding the cleavage of the thiazole ring of benzothiazoles was the reductive cleavage of the thiazole ring by metallic sodium in liquid ammonia reported by Knowles and Watt.⁽⁷⁾ Mills *et al.*⁽⁸⁾ also reported that pseudo bases derived from benzothiazolium salts could be converted into mercaptoformamide compounds by means of aqueous alkali. These reports indicate the cleavage of carbon-sulfur bond in $-S-\overset{|}{C}=N-$ linkages and especially, the latter is of importance because it suggests the cleavage by hydrolysis.



Thus, mechanism of the cleavage of 2-aminothiazolo[5,4-*b*]pyridines may be interpreted as follows :



R= H, Cl, CH_3O, C_2H_5O etc.

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6) A. W. Hofmann : Ber., **12**, 2360(1879); **13**, 20(1880); **20**, 2251(1887); A. Kwaysser : Ann., **277**, 242(1893); A. I. Kiprianov, Z. N. Pazenko : J. Gen. Chem. **19**, 1523(1949); C. A., **44**, 3487(1950).

7) C. M. Knowles, G. W. Watt : J. Org. Chem., **7**, 56(1942).

8) W. H. Mills, L. M. Clark, J. A. Aeschlimann : J. Chem. Soc., **123**, 2353(1923).

In the first place, hydroxyl ion attacks the carbon at 2-position of 2-aminothiazolo[5, 4-*b*]pyridines, and through a transition state of type (XI), the linkage between the carbon at 2-position of the thiazole ring and sulfur undergoes cleavage to bring about the formation of the urea compound which affords 2-mercapto-3-aminopyridines on hydrolysis. Moreover, it was found that the rate of the conversion of thiazolopyridine into the urea product was fast, while the latter step proceeded slowly.

The author is grateful to Prof. T. Takahashi for his kind and unfailing guidance through the course of this work. He is indebted to Dr. H. Kano and Mr. A. Narisada of the Research Laboratory, Shionogi & Co. Ltd., for the measurement of the infrared spectra, to Messrs. S. Matsuo and E. Yoshii of the Research Laboratory, Nippon Shinyaku Co. Ltd., for the measurement of the ultraviolet spectra, and to the members of the analytical center of the University of Kyoto for the microanalyses. The author is also grateful to Messrs. J. Iwai and R. Okada for cooperation in this work.

Experimental*

6-Chloro-2-mercaptopyridyl-3-urea (VI)—In 170 cc. of glacial AcOH was dissolved 1.2 g. of 3-amino-6-chloro-2-mercaptopyridine (I). To this solution was added slowly with stirring a solution of 2.5 g. of KNCO in 20 cc. of water at 40°. After a continued stirring for 3 hrs., the reaction mixture was diluted with a large amount of water and allowed to stand over night. The precipitated solid was filtered with suction. The yield of crude (VI), pale yellow crystalline powder, was 0.82 g. It was recrystallized from glacial AcOH, washed consecutively with aq. $NaHCO_3$ and H_2O, and dried, yielding pale yellow granules, m.p. 185~190°(effervescence). *Anal.* Calcd. for $C_6H_6ON_3ClS$: C, 35.38; H, 2.95; N, 20.64. Found : C, 35.68; H, 2.98; N, 20.88.

6-Chloro-2-methylthiopyridyl-3-urea (VII)—a) A solution of 0.8 g. of 3-amino-6-chloro-2-methylthiopyridine (III) in 12 cc. of glacial AcOH and 6 cc. of water was treated with a solution of 1.2 g. of KNCO in 5 cc. of water at 35°. About a half of KNCO solution was added slowly with stirring until a white crystalline precipitate appeared. The rest was then added quickly with vigorous agitation. The resulting suspension was stirred for a further 10 mins., allowed to stand at room temperature for 2~3 hrs., and diluted with water. After cooling to 0°, the material was filtered with suction, washed with water, and dried. Recrystallization from MeOH afforded 0.8 g. of white scales or needles. The substance melted indefinitely at 286~295°. U.V. λ_{max}^{EtOH} 220, 262, 309 mμ (log ε 4.19, 4.10, 3.86). *Anal.* Calcd. for $C_7H_8ON_3ClS$: C, 38.62; H, 3.68; N, 19.31. Found : C, 38.79; H, 3.78; N, 19.26.

b) Methylation of (VI) with CH_3I in alkaline medium furnished the same product (VII).

6-Ethoxy-2-methylthiopyridyl-3-urea (VIII)—A solution of 0.46 g. of 3-amino-6-ethoxy-2-methylthiopyridine in 7 cc. of glacial AcOH and 3 cc. of water was treated with a solution of 0.7 g. of KNCO in 3 cc. of water in the same manner as in (VI). Recrystallization was effected from EtOAc to give white scales, which melted indefinitely at 200~236°. U.V. λ_{max}^{EtOH} 253, 304 mμ (log ε 4.08, 3.91). Yield, 0.32 g. *Anal.* Calcd. for $C_9H_{13}O_2N_3S$: C, 47.56; H, 5.76; N, 18.48. Found : C, 47.63; H, 5.67; N, 18.45.

6-Ethoxy-2-ethylthiopyridyl-3-urea (IX)—This substance was obtained in the same manner as (VIII). Colorless needles, m.p. 160~161°. U. V. λ_{max}^{EtOH} 253, 305 mμ (log ε 4.36, 4.19). *Anal.* Calcd. for $C_{10}H_{15}O_2N_3S$: C, 49.77; H, 6.26; N, 17.41. Found : C, 49.60; H, 6.20; N, 17.45.

Acetylation of 6-Chloro-2-methylthiopyridyl-3-urea (VII) by Ac_2O—6-Chloro-2-methylthiopyridyl-3-urea (0.6 g.) was heated with 40 cc. of Ac_2O on a boiling water bath for 6 hrs. The resulting solution was evaporated to dryness *in vacuo* and the residue was once recrystallized from EtOH, giving N'-acetyl-N-(6-chloro-2-methylthiopyridyl-3)urea (V) (80 mg.). A sample was recrystallized several times from EtOH to give colorless needles, m.p. 209°. *Anal.* Calcd. for $C_9H_{10}O_2N_3ClS$: C, 41.65; H, 3.85; N, 16.20. Found : C, 41.98; H, 4.04; N, 15.90. The filtrate of the first recrystallization was freed from solvent and the residue was taken up in 25 cc. of $CHCl_3$. The solution was then passed through a short column of alumina, followed by more $CHCl_3$. The eluate was evaporated on a water bath and the residue was recrystallized from MeOH to colorless thin plates or needles, m.p. 166°, undepressed on admixture with 3-acetamido-6-chloro-2-methylthiopyridine prepared by acetylation of (III). Yield, 300 mg. U.V. λ_{max}^{EtOH} 220, 260, 304 mμ (log ε 4.10, 4.08, 3.86).

Hydrolysis of 6-Chloro-2-mercaptopyridyl-3-urea (VI)—a) A solution of 0.7 g. of (VI) in 6 cc. of 10% NaOH was refluxed in an oil bath (120~130°) for 1 hr., and after 5 mins., the evolution of NH_3 increased. The solution was neutralized with aq. AcOH and the precipitated product was filtered with suction. Yield, 0.6 g. Subsequently, the product was methylated with Me_2SO_4 in the usual manner. The deposited crystals were collocted by filtration and extracted with the minimum

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* All melting points are uncorrected.

amount of ether. The ether extract on evaporation gave (III), which after recrystallization from a mixture of petr. ether and ether formed colorless needles, m.p. and mixed m.p. 56°. The residue from the ether extract, after recrystallization from MeOH, afforded (VII) as white scales, m.p. and mixed m.p. 290°. The yields of (III) and (VII) were 0.15 g. and 0.12 g., respectively.

b) Six hrs.' boiling of (VI), after methylation of the product, afforded only (III).

Cleavage of 2-Aminothiazolo[5,4-*b*]pyridines with aq. NaOH: Cleavage of 2-Amino-5-chlorothiazolo[5,4-*b*]pyridine—a) One hr.'s reaction of 0.7 g. of the thiazolopyridine with 6 cc. of 10% NaOH and subsequent methylation with Me_2SO_4 gave 0.21 g. of (III) and 0.22 g. of (VII) which were fractionated in the same manner described above.

b) 7 hrs.' reaction of the thiazolopyridine by a similar procedure furnished only (III). This fact indicates that for the preparation of pure 3-amino-6-chloro-2-mercaptopyridine, 7 hrs. seem preferable. Also, since in the use of aq. NaOH, the precipitated mercapto-aminopyridine was contaminated with a large amount of inorganic substance and did not show any distinct m.p., the following procedure for the purification was undertaken: The crude (I) was dissolved in aq. $Ba(OH)_2$, reprecipitated with AcOH after filtration, and washed with H_2O, whereby it was obtained pure as yellow crystalline powder, m.p. 185°(effervescence).

Cleavage of 2-Amino-5-ethoxythiazolo[5,4-*b*]pyridine—One g. of the thiazolopyridine was heated under reflux with 10 cc. of 20% NaOH in the presence of 0.2 g. of As_2O_3 for 6.5 hrs. After the lapse of 10 mins., the evolution of ammonia became remarkable. After cooling, the resulting clear solution was filtered with suction and neutralized with AcOH. The precipitate was dissolved in aq. $Ba(OH)_2$, reprecipitated with AcOH after filtration, and washed with H_2O, yielding a yellow crystalline powder which melted indefinitly at 150~170°. Yield, 0.7 g. This substance was 3-amino-6-ethoxy-2-mercaptopyridine (II).

For the characterization, a sample was methylated with Me_2SO_4 in alkalin medium, yielding 3-amino-6-ethoxy-2-methylthiopyridine as an oil. Subsequently, acetylation afforded 3-acetamino-6-ethoxy-2-methylthiopyridine, m.p. 124°, undepressed on admixture with an authentic sample. The neutralized filtrate, after being allowed to stand over night, afforded 0.1 g. of 6-ethoxy-2-mercaptopyridyl-3-urea (X), m.p. 195~198°(decomp.), which was characterized by the fact that methylation with Me_2SO_4 furnished (VIII). Also, 3-amino-6-ethoxy-2-mercaptopyridine obtained by 10 hrs.' boiling with aq. NaOH was sufficiently pure for further synthetic work.

6-Ethoxy-2-phenylpyrido[2,3-*b*]-1,4-thiazine—In a solution of 1 cc. of water and 5 cc. of EtOH containing 0.2 g. of NaOH, 0.5 g. of 3-amino-6-ethoxy-2-mercaptopyridine was dissolved. To this solution was added 0.6 g. of phenacyl bromide and the reaction mixture was allowed to stand at room temperature over night. The precipitate thus obtained was collected by filtration and recrystallized from MeOH to pale yellow needles, m.p. 125°, undepressed on admixture with a sample prepared as described in Part XLII.[3] Yield, 0.42 g.

Summary

1) The structure of the unknown substances (Substances I, II, and III) described in Part XXXVIII were determined as 6-chloro-2-methylthiopyridyl-3-urea, 6-ethoxy-2-methylthiopyridyl-3-urea, and 6-ethoxy-2-ethylthiopyridyl-3-urea, respectively.

2) Mechanism of cleavage of the 2-aminothiazolo[5,4-*b*]pyridines was studied.

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