U.D.C. 547.825

78. Kan-ichi Ueda : Sulfur-containing Pyridine Derivatives. LI*. 2,6-Diamino-3-mercaptopyridine Derivatives.

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An earlier work of this series showed that 2,5-diaminothiazolo[4,5-*b*]pyridine, when allowed to reflux with aqueous sodium hydroxide, gave 2,6-diamino-3-mercaptopyridine, and that some derivatives of the aminopyridinethiol were prepared. According to the result of later investigation, it was found that the above-mentioned work involved some interesting problems as follows : (1) Mechanism of the cleavage of the thiazole ring and behavior of the amino group in the 5-position of 2,5-diaminothiazolo-[4,5-*b*]pyridine by refluxing with aqueous alkali; (2) methylation of 2,6-diamino-3-mercaptopyridine with dimethyl sulfate in alkaline medium; and (3) acetylation of 2,6-diamino-3-methylthiopyridine with acetic anhydride.

This paper acts as a supplement to Part XXXVIII[1] and describes the results of reëxamination on the above problems.

In the previous paper[2] of this series, it was shown that the cleavage of 2-aminothiazolo[5,4-*b*]pyridines with alkali proceeded in accordance with the following steps; thiazolopyridine → mercaptopyridylurea → amino-mercaptopyridine, where mercaptopyridylurea was hydrolyzed with comparative difficulty to give amino-mercaptopyridine.

The cleavage reaction of 2,5-diaminothiazolo[4,5-*b*]pyridine (I) was again performed in comparison with [5,4-*b*] series. On the other hand, it is generally known that the amino group in the α- or γ-position of pyridine ring is replaced with hydroxyl group by refluxing with aqueous alkali.[3] Therefore, greatly prolonged heating must be avoided if possible in the case of alkaline cleavage reaction of (I). However, experimental results indicated that one hour's cleavage reaction of (I) gave 2,6-diamino-3-mercaptopyridine (II) which reacted with dimethyl sulfate forming the expected S-methyl ether only, being different from that of [5,4-*b*] series. Thus, it may well be concluded that the cleavage of the thiazole ring of (I) can be achieved in comparatively short reaction time to give final product (II) without replacement of 5-amino group of (I) with hydroxyl group.

Subsequently, when the product of cleavage of (I) without isolation was treated with dimethyl sulfate, the methylated oily product was obtained. If methylation takes place at either ring-nitrogen or amino group of (II), Grote's color reaction of the product thereby obtained might be positive, and moreover, its oxidation product should be soluble in alkali on account of the conversion of thiol compound to sulfinic acid compound. By Grote's reagent, the methylated product did not show any color, and after a few steps, acetylation, oxidation, and hydrolysis, it gave methyl 2,6-diaminopyridyl-(3) sulfone (IV) which was insoluble in alkali. Therefore, it is proved to be 2,6-diamino-3-methylthiopyridine (III).

In Part XXXVIII, the author reported that when (III) was treated with acetic anhydride in the refluxing temperature, 2,6-diacetamido-3-methylthiopyridine (VI) was

* This work is a part of series entitled "Sulfur-containing Pyridine Derivatives" by Torizo Takahashi. Part L : This Bulletin, **4**, 396(1956).

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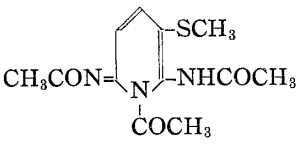
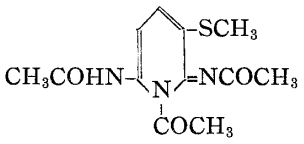
1) T. Takahashi, K. Ueda : J. Pharm. Soc. Japan, **73**, 442(1953).
2) K. Ueda : This Bulletin, **4**, 396(1956).
3) E. Koenigs, M. Mields, H. Gurlt : Ber., **57**, 1179(1924); H. Saikachi : J. Pharm. Soc. Japan, **64**, 201(1944).

produced; however, it was found that the acetate was not (VI) but a triacetate (V) from analytical data (especially, analysis of nitrogen), which was easily hydrolyzed to give diacetate (VI), m.p. 181°, by dissolving in 10% aqueous alkali. The diacetate, when again treated with acetic anhydride, converted to the original triacetate. Accordingly, the structure of the triacetate must be formulated by either (Va) or (Vb) as follows[4]:



(Va)



(Vb)

Subsequently, it is evident that the formation of the diacetate by hydrolysis is caused by the removal of one acetyl group among three acetyl groups represented in the above formulae. In order to confirm the structure of the diacetate, the comparison of ultraviolet absorption spectra (Fig. 1) of (V) and (VI) was made, including that of 2,6-diacetamidopyridine.[5]

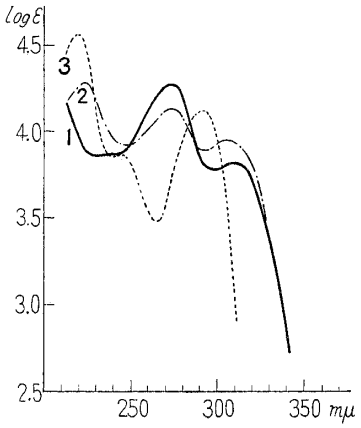


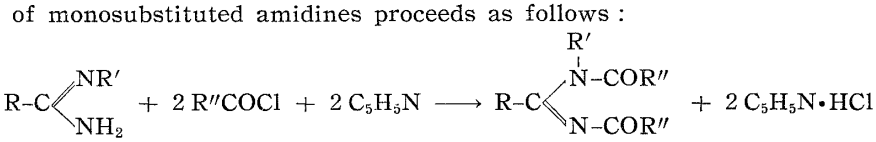
Fig. 1.
Ultraviolet Absorption Spectra

1. Triacetate (V)
2. Diacetate (VI)
3. 2,6-Diacetamidopyridine

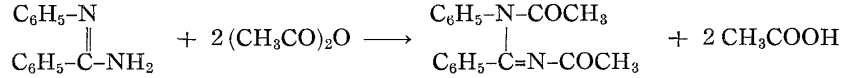
Hydrolysis of acetamido or acetimido group of (V) results in the formation of the product containing amino or imino group. Therefore, it would be expected that the appearance of these groups causes a bathochromic shift at longer wave length; however, the spectrum of (VI) does not show any bathochromic shift as compared with that of (V). Consequently, it may be considered that (VI) is 2,6-diacetamido-3-methylthiopyridine.

Oxidation of (VI) with potassium permanganate proceeded in acetic acid at room temperature to afford the corresponding sulfone (VII), which was identical with that reported in Part XXXVIII. (V) was also easily oxidized to methyl 2(or 6)-acetamido-6 (or 2)-acetimido-N-acetylpyridyl-(3) sulfone (VIII). The relationship similar to that of (V) and (VI) was also observed between (VII) and (VIII). These sulfones, (VII) and

4) Acylation of monosubstituted amidines proceeds as follows:



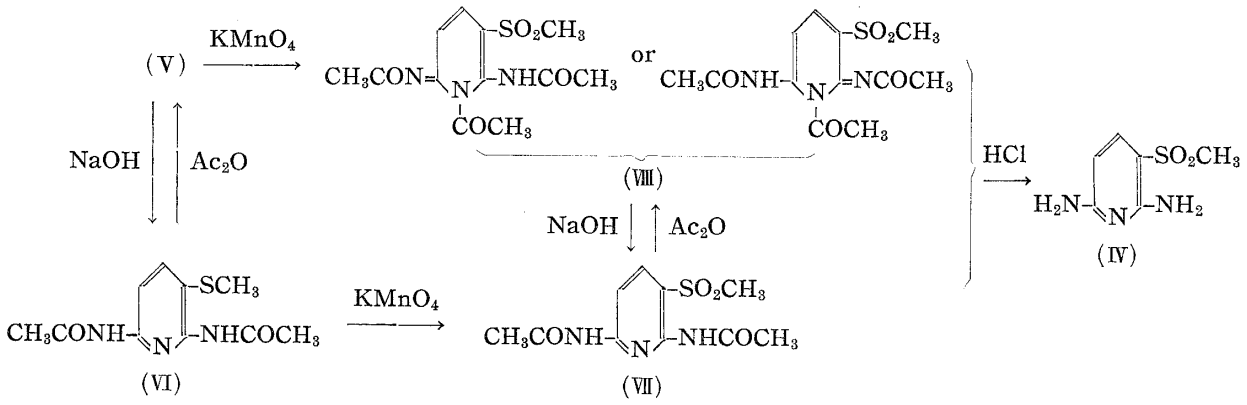
cf. R. Walther, R. Grossmann: J. prakt. Chem., [2], **78**, 478(1908); H. L. Wheeler, *et al.*: J. Am. Chem. Soc., **25**, 790(1903).



cf. A. Lottermoser: J. prakt. Chem., [2], **54**, 116(1897).

5) A. E. Chichibabin, O. A. Seide: Chem. Zentr., **1923**, III, 1022.

(VIII), were hydrolyzed with conc. hydrochloric acid to give (IV) together. The relationship among these is shown in the following chart.



The author expresses his gratitude to Prof. T. Takahashi for his kind advices and encouragement. The author is also indebted to Mr. S. Matsuo of the Research Laboratory, Nippon Shinyaku Co. Ltd., for the measurement of ultraviolet spectra, and to the members of the Microanalytical Laboratory of this Institute for the microanalyses.

Experimental[6]

2(or 6)-Acetamino-6(or 2)-acetimido-N-acetyl-3-methylthiopyridine (V)—2,5-Diaminothiazolo[4,5-*b*]pyridine (I) (1.7 g.) was suspended in aq. NaOH solution (20 cc. of 10%) and the whole was refluxed in an oil bath kept at 130~140°. After 1 hr.'s heating, all the thiazolopyridine disappeared, giving a yellowish solution. On cooling, the resultant solution was once filtered by suction, and then to the filtrate was added dropwise Me_2SO_4 (1.4 g.). The reaction proceeded with evolution of heat. After being allowed to stand for several hrs., the oil that separated was throughly extracted with ether. The ether was washed with water, dried over K_2CO_3, and evaporated. There remained a yellow transparent syrup, presumably 2,6-diamino-3-methylthiopyridine, which showed a negative color reaction to Grote's reagent.

This syrup was dissolved in an excess of Ac_2O and the solution was refluxed for 1 hr. After being heated, the solution was evaporated in vacuum, leaving a syrup which, on addition of EtOH, solidified. The resultant crystalline solid was collected and then recrystallized from EtOH, forming colorless needles, m.p. 178°. Yield, 0.9 g. *Anal.* Calcd. for $C_{12}H_{15}O_3N_3S$: C, 51.35; H, 5.37; N, 14.94. Found: C, 51.54; H, 5.49; N, 15.37.

2,6-Diacetamido-3-methylthiopyridine (VI)—When the solution of (V) in 10% NaOH was neutralized with AcOH crystalline solid precipitated. Recrystallization of the product from EtOH-AcOEt mixture formed colorless crystals, m.p. 180~181°. *Anal.* Calcd. for $C_{10}H_{13}O_2N_3S$: C, 50.22; H, 5.44; N, 17.56. Found: C, 50.15; H, 5.52; N, 17.36.

Oxidation of (V) and (VI)—To a solution of (V) in glacial AcOH was added dropwise a sat. aq. solution of $KMnO_4$ with stirring at room temperature. After continued stirring for several hrs., 30% H_2O_2 was added to the reaction mixture to dissolve the resulting precipitate of MnO_2. The clear solution thus obtained was concentrated under reduced pressure and addition of a small amount of water to the residue afforded the crude product (VIII). It was recrystallized from MeOH forming colorless granules, m.p. 190~191°. *Anal.* Calcd. for $C_{12}H_{15}O_5N_3S$: N, 13.41. Found: N, 13.71.

Similar oxidation of (VI) with $KMnO_4$ gave (VII), which was recrystallized from EtOH to afford colorless needles, m.p. 248°. It showed no melting point depression on admixture with a sample prepared as described in Part XXXVIII.[1] This substance was also obtained by neutralizing the solution of (VIII) in 10% NaOH with AcOH.

When these sulfones, (VII) and (VIII), were heated with conc. HCl on a boiling water bath for 1 hr., (IV) was obtained, which was recrystallized from benzene-AcOEt mixture forming pale yellow pillars, m.p. 183°. This substance was insoluble in alkali. *Anal.* Calcd. for $C_6H_9O_2N_3S$: C, 38.49; H, 4.85; N, 22.45. Found: C, 38.77; H, 4.80; N, 22.27.

Ultraviolet Spectra—Spectra were determined with a Beckman model DU quartz spectrophotometer in abs. EtOH.

6) All melting points are uncorrected.

Compound	λ_{max}	log ϵ
2(or 6)-Acetamido-6(or 2)-acetimido-N-acetyl-3-methylthiopyridine	(234)	3.86
	272	4.28
	310	3.82
2,6-Diacetamido-3-methylthiopyridine	223	4.29
	274	4.13
	306	3.96
2,6-Diacetamidopyridine	220	4.57
	244	3.86
	291	4.13

Summary

1) In Part XXXVIII, it was reported that when 2,6-diamino-3-methylthiopyridine (III) was refluxed with acetic anhydride, 2,6-diacetamido-3-methylthiopyridine (VI) was produced. However, it was found that this acetate was a triacetate, the structure of which must be represented by either 2-acetamido-6-acetimido-N-acetyl-3-methylthiopyridine (Va) or 6-acetamido-2-acetimido-N-acetyl-3-methylthiopyridine (Vb), and the relationship between the diacetate (VI) and the triacetate (V) was investigated.

2) Oxidation products of (V) and (VI) were obtained.

(Received June 18, 1956)