*The Tautomerism and Methylation of 3, 6-Disubstituted Pyridazines**

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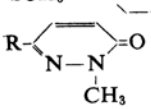
The tautomerism of heteroaromatic compounds containing two different potentially tautomeric groups has not been widely studied. A recent investigation of 4-amino-6-hydroxypyrimidine and its related compounds reported by Brown and Harper[1] represents the only published case in which a 6-hydroxyl group exists predominantly in the keto form. This paper will deal with the tautomerism of 3, 6-disubstituted pyridazines which contain two different potentially tautomeric groups, such as OH, SH and NH_2. Furthermore, the attempted methylation of 3,6-disubstituted pyridazines will be discussed in connection with their tautomeric forms.

TABLE I. IONIZATION CONSTANTS OF SUBSTITUTED PYRIDAZINES, IN WATER AT 20°C

Compound R	Compound R′	Acidic pK_a	Basic pK_a
SH	OH	3.32	−1.39
SCH_3	OH	10.11*	(−)
SH	OCH_3	6.95*	−2.36
SCH_3	OCH_3	—	1.84
Cl	NH_2	—	3.85
SH	NH_2	9.05*	−0.14
SCH_3	NH_2	—	5.61
Cl	$NHCH_3$	—	4.01
SH	$NHCH_3$	9.46*	−0.04
SCH_3	$NHCH_3$	—	5.94
Cl		—	3.51
SH		9.31	−0.06
SCH_3		—	5.13
			
R			
OH		5.46*	−1.32
SCH_3		—	(−)

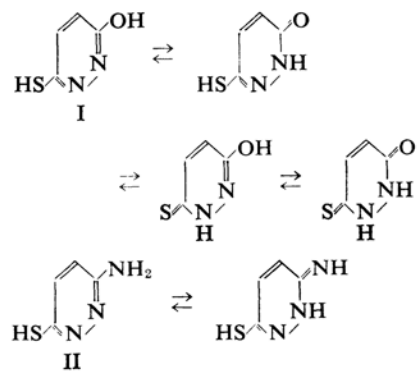
* These values were obtained by potentiometric titration and the values without asterisk were measured by means of spectrophotometric method. (−) means that spectrophotometric method did not allow to give pK_a value.

* Part of the data given in this article were presented at the 16th Annual Meeting of the Chemical Society of Japan, Tokyo, April, 1963.

Results and Discussion

The compounds studied in this work are listed in Table I, together with their ionization constants in aqueous solutions. These compounds were prepared by the method shown in Fig. 1, and their pK_a values were determined by potentiometric titration or the spectrophotometric method.[2]

Preferred Tautomeric Forms. — The conceivable tautomeric forms for 3-hydroxy-6-mercaptopyridazine (I)[3] and 3-amino-6-mercaptopyridazine (II)[4] in aqueous solutions may be written as follows:



I

II

1) D. J. Brown and J. S. Harper, *J. Chem. Soc.*, **1961**, 1298.
2) L. A. Flexser, L. P. Hammett and A. Dingwall, *J. Am. Chem. Soc.*, **57**, 2103 (1935).
3) J. Druey, Kd. Meier and K. Eichenberger, *Helv. Chim. Acta*, **37**, 121 (1954).
4) H. G. Morren, Belg. Pat. 579291 (1959).

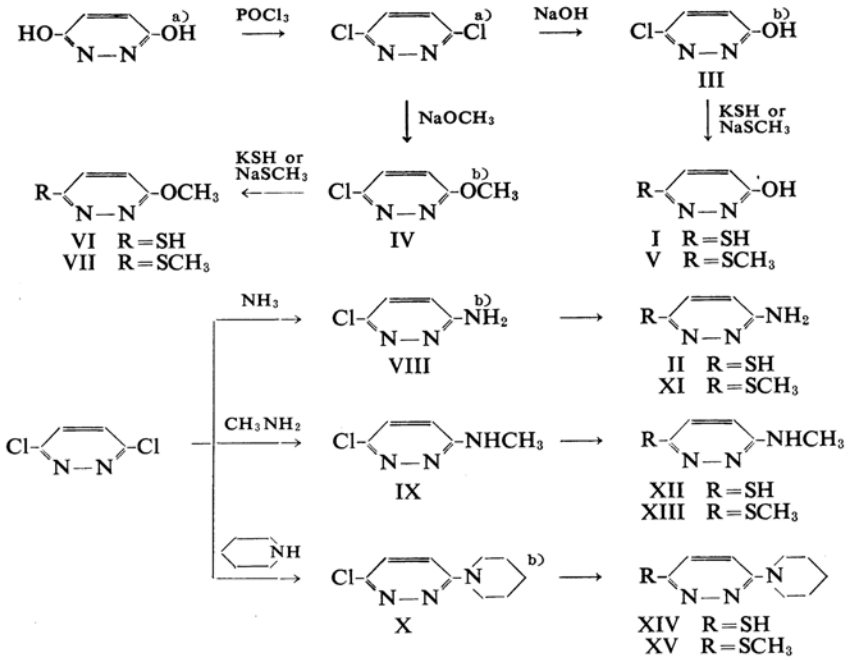
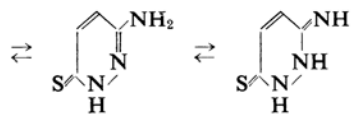


Fig. 1. The synthesis of the compounds.

a) R. H. Mizzoni and P. E. Spoerri, *J. Am. Chem. Soc.*, **73**, 1873 (1951).

b) J. Druey, Kd. Meier and K. Eichenberger, *Helv. Chim. Acta*, **37**, 121 (1954).



These compounds are also capable of existing in three forms, i. e., the neutral, anionic and cationic forms, depending on the pH values of the solutions. In the pH regions above the acidic values and below the basic values of their pK_a's, these compounds would be largely in the anionic and cationic forms respectively. In the pH range between the acidic and basic values of their pK_a's, these compounds would predominantly be in neutral forms and exhibit the tautomeric equilibria shown above.

In order to assign the preferred tautomer of 3-hydroxy-6-mercaptopyridazine (I) in an aqueous solution, the ultraviolet spectrum of the neutral species of I measured at pH 3.02 was compared with that of 3-mercapto-6-methoxypyridazine (VI) in which the tautomerism of the hydroxyl group of I had been inhibited. The spectra of the two compounds closely resemble each other in shape, as is shown in Fig. 2. Thus, it is highly probable that the lactim form predominates over the lactam form in the tautomerism of I. Furthermore, since the spectrum of I is markedly different from that of 3-methoxy-6-methylthiopyridazine (VII), the proportion of the thiolactam form of I should be very large. However,

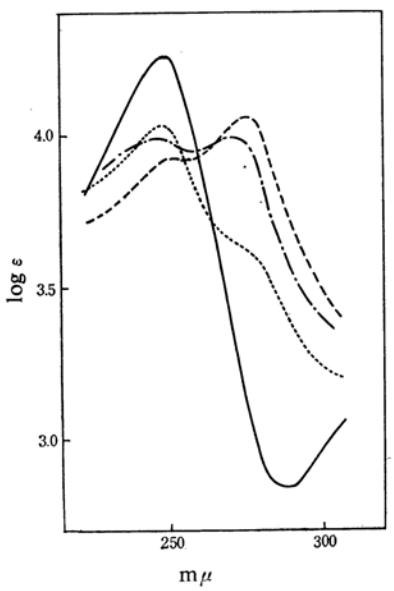


Fig. 2. Ultraviolet absorption spectra of neutral species in the aqueous solution;

---- 3-hydroxy-6-mercaptopyridazine (I) (pH 3.02),

---- 6-mercapto-3-methoxypyridazine (VI) (pH 2.87),

—— 3-hydroxy-6-methylthiopyridazine (V) (pH 6.28) and

------ 3-methoxy-6-methylthiopyridazine (VIII) (pH 5.38).

the spectrum of the neutral species of 3-hydroxy-6-methylthiopyridazine (V) differs from that of the compound VII. This seems to mean that V exists predominantly in the lactam form.

For assigning the preferred tautomers of 3-amino-6-mercaptopyridazine (II), 3-mercapto-6-methylaminopyridazine (XII) and 3-mercapto-6-piperidinopyridazine (XIV) in aqueous solutions, the tautomerism between amino and imino forms for II and XII was first examined. The ultraviolet absorption spectra of 3-amino-6-chloropyridazine (VIII) and 3-chloro-6-methylaminopyridazine (IX) were measured and compared with that of 3-chloro-6-piperidinopyridazine (X), in which the tautomeric hydrogen atom is lacking. The spectra of VIII, IX and X closely resemble one another in shape, as may be seen in Fig. 3.

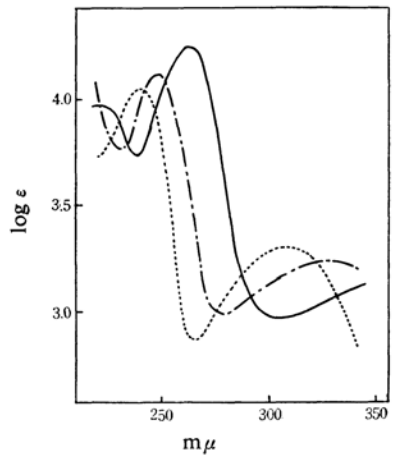


Fig. 3. Ultraviolet absorption spectra of neutral species in the aqueous solution;
------ 3-amino-6-chloropyridazine (VIII) (0.1N NaOH),
—·— 6-chloro-3-methylaminopyridazine (IX) (0.1N NaOH) and
—— 6-chloro-3-piperidinopyridazine (X) (0.1N NaOH).

Therefore, the amino group of II and the methylamino group of XII may exist predominantly in the amino and methylamino forms respectively. The marked differences which appeared in the spectra of the neutral species of the three pairs, II and XI, XII and XIII, and XIV and XV, (cf. Fig. 4), provide strong evidence that II, XII and XIV exist predominantly in the thiolactam forms rather than in thiol forms in aqueous solutions.

The Infrared Spectra of Substituted Pyridazines. — The infrared spectra of substituted pyridazines were measured in the solid states to verify the above conclusions. The results

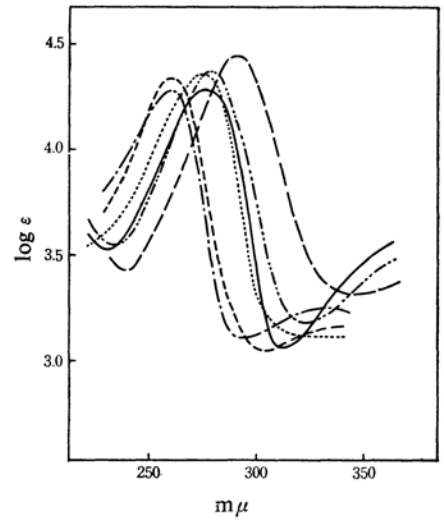


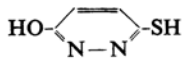
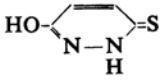
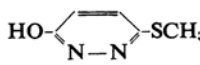
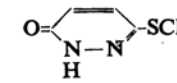
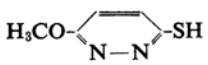
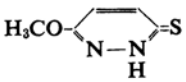
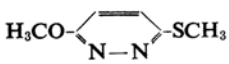
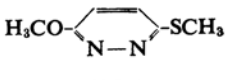
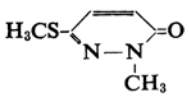
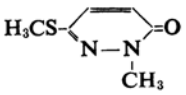
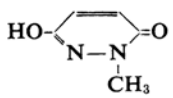
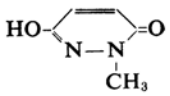
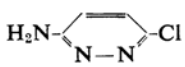
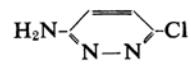
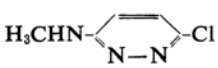
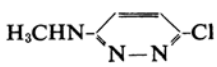
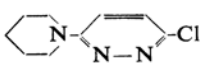
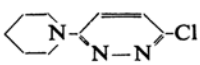
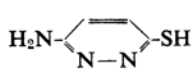
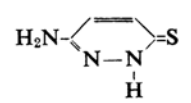
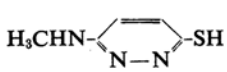
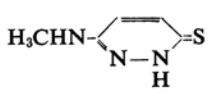
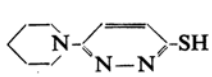
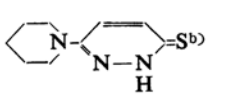
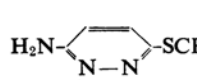
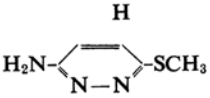
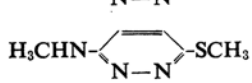
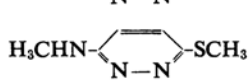
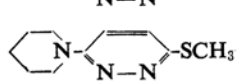
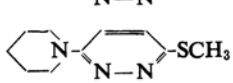
Fig. 4. Ultraviolet absorption spectra of neutral species in the aqueous solution;
—— 3-amino-6-mercaptopyridazine (II) (pH 5.38),
– – – 3-amino-6-methylthiopyridazine (XI) (pH 6.28),
····· 3-methylamino-6-mercaptopyridazine (XII) (pH 5.38),
– – – – 3-methylamino-6-methylthiopyridazine (XIII) (pH 6.28),
—·— 6-mercapto-3-piperidinopyridazine (XIV) (pH 6.33) and
------ 6-methylthio-3-piperidinopyridazine (XV) (0.1N NaOH).

are summarized in Table II. As Table II illustrates, the structures of pyridazine derivatives in the solid states may be presumed to be identical with those of the neutral species suggested above in aqueous solutions.

The Ultraviolet Absorption Spectra of I and II in Various Solvents. — Since tautomerism is known to be affected by the nature of the solvents, the ultraviolet absorption spectra of I and II were measured in various solvents with different dielectric constants. Figure 5 shows that the absorption maxima shift toward the longer wavelength region with the decrease in dielectric constants for the solvents used.

Methylation of Compounds I and II. — The methylation of I and II with methyl iodide or dimethyl sulfate was studied. The results are listed in Table III. The thiol groups of I and II were found to be methylated more readily than the amino or the hydroxy groups under any conditions examined. However, when the methylation of I was carried out with dimethyl sulfate under the conditions described in Table III, a compound with an m.p. of 27~29°C, (XVI), was obtained as the major product. The results of the elementary analysis of XVI were in agreement with the calculated values

TABLE II. INFRARED SPECTRA OF SUBSTITUTED PYRIDAZINES

Compound	$\nu_{C=N}$ or $\nu_{C=C}$ cm^{-1}	$\nu_{C=O}$ cm^{-1}	ν_{N-H} cm^{-1}	$\nu_{C=S}$ [a] cm^{-1}	Assumed structure
	1529 s	—	—	1086 s	
	1591 s	1713 s	—	—	
	1567 s	—	—	1080m	
	1597 s	—	—	—	
	1619 s 1575 s	1661 s 1644 s	—	—	
	1600 s	1671 s	—	—	
	1656 s 1608 s	—	3435 s 3231 s	—	
	1617 s	—	3264 s	—	
	1587 s	—	—	—	
	1653 s 1631m 1576 s	—	3585 s 3518 s 3400m sh 3288m	1126 s	
	1627m	—	3241m 3110m	1143 s	
	1612w	—	3160m 3100m	?	
	1641 s 1619 s	—	3312m 3140m	—	
	1621 s	—	3353m 3245m	—	
	1593 s	—	—	—	

Estimated band intensities are given as strong (s), medium (m) and weak (w), and a shoulder band is shown as (sh). a) E. Spinner, *J. Chem. Soc.*, **1960**, 1237. b) The structure of this compound was not certain because $\nu_{C=S}$ could not be found for this compound.

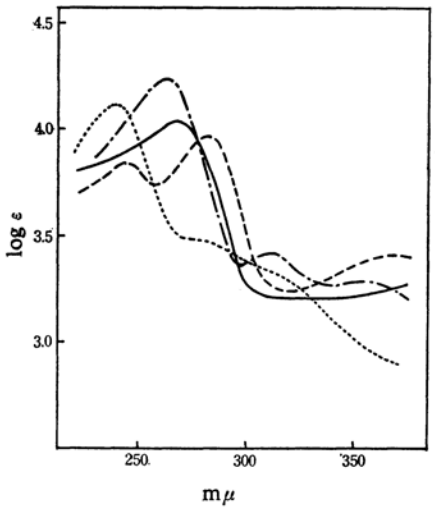


Fig. 5-a. Ultraviolet absorption spectra of 3-hydroxy-6-mercaptopyridazine;
---- in ethanol, —— in ethanol-water 1 : 1, —·— in water and ------ in 40% sulfuric acid.

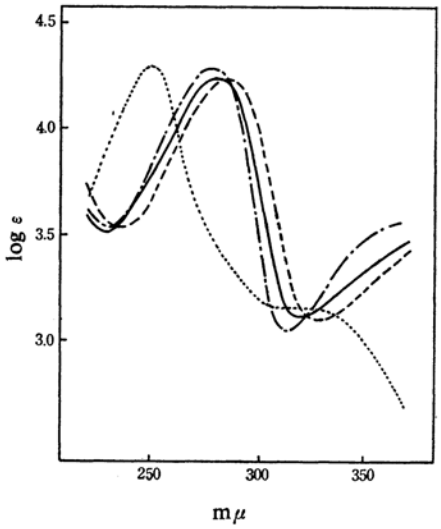


Fig. 5-b. Ultraviolet absorption spectra of 3-amino-6-mercaptopyridazine; ---- in ethanol, —— in ethanol-water 1 : 1, —·— in water and ------ in 20% sulfuric acid.

for the dimethylated compound of I. The spectrum of the neutral species of XVI closely resembles that of the neutral species of 3-hydroxy-6-methylthiopyridazine (V), the preferred tautomeric form of which was proposed in a previous section of this paper to be the lactam form (see Fig. 6).

The infrared spectrum of XVI shows a very strong absorption band at 1682 cm^{-1} due to carbonyl stretching vibration. On the basis of these results, the most reasonable structure assigned for XVI seems to be 2-methyl-6-methylthio-2, 3-dihydropyridaz-3-one.

Table III. Methylation of I and II

Compound	Methylating agent	Solvent	Added base	Reaction		Product	Yield %
				Temp. °C	Time hr.		
I	CH_3I[a]	CH_3OH	$NaOCH_3$	70	1	V	78
I	CH_3I[b]	CH_3OH	$NaOCH_3$	120	2	V	72
I	CH_3I[a]	CH_3OH - H_2O	$NaHCO_3$	75	1	V	63
I	$(CH_3)_2SO_4$[a]	—	—	100	1	V	72
						XVI	8
I	$(CH_3)_2SO_4$[b]	—	—	140	3	XVI	80
II	CH_3I[a]	CH_3OH	$NaOCH_3$	reflux	1	XI	63
II	CH_3I[b]	CH_3OH	$NaOCH_3$	75	1	XI	72
II	CH_3I[a]	CH_3OH - H_2O	$NaHCO_3$	reflux	1	XI	81

a) The molar ratio of methylating agent to I or II was 1.
b) The molar ratio of methylating agent to I or II was 2.

Table IV. 3-Substituted 6-mercaptopyridazines

3-Substituent	Reaction condition		Yield %	M. p. °C	Analysis N%	
	Temp., °C	Time, hr.			Calcd.	Found
$-OCH_3$	135~145	6	57	191~193	19.70	19.34
$-NHCH_3$	80~ 90	3	52	234~237 (decomp.)	29.77	29.87
	170~180	9	76	147~149	21.52	21.07

Recrystallization were carried out with the following solvents; $-OCH_3$: aqueous ethanol, $-NHCH_3$: water,  : water.

TABLE V. 3-SUBSTITUTED 6-METHYLTHIOPYRIDAZINES

3-Substituent	Reaction condition Temp., °C	Time, hr.	Yield %	M. p. °C	Analysis N% Calcd.	Found
-OH	140~160	6	60	132~133	19.70	20.28
$-OCH_3$	140~160	6	65	85~ 87	17.94	18.21
$-NH_2$	120~130	9	70	116~117	29.77	30.27
$-NHCH_3$	130~140	8	83	83~ 84	27.08	27.12
-N⟨⟩	170~180	9	60	77~ 79	20.08	20.04

Recrystallizations were carried out with the following solvents; -OH and $-OCH_3$: water, $-NH_2$: benzene, $-NHCH_3$: ligroin, -N⟨⟩: cyclohexane.

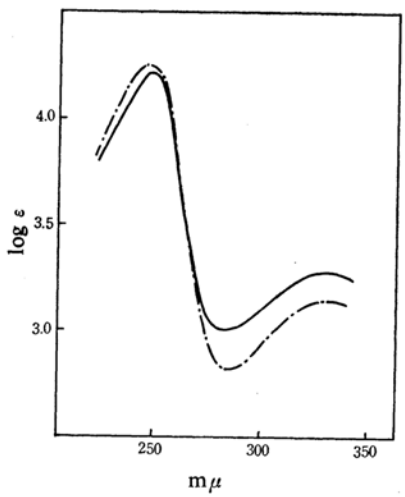


Fig. 6. Ultraviolet absorption spectra of neutral species in the aqueous solution;
—— 2-methyl-6-methylthio-2, 3-dihydropyridaz-3-one (XVI) (0.1 M H_2SO_4),
---- 3-hydroxy-6-methylthiopyridazine (V) (0.1M H_2SO_4).

Experimental

The Measurement of pK_a's Values.—pK_a values for the compounds which were soluble in water were measured by potentiometric titration, and those for the compounds which were sparingly soluble in water, by the spectrophotometric method.

The Measurement of the Ultraviolet Spectra.—The ultraviolet spectra were measured with a Hitachi EPS-2 spectrophotometer. The measurements were made in buffered, acidic or alkaline solutions and the pH value of each solution was adjusted so that more than 99% of the compound might exist in the form of neutral, cationic or anionic species in the solution, as expected from the pK_a values for the compound.

The Measurement of Infrared Spectra. — The infrared spectra were recorded with a Hitachi EPI-2 spectrophotometer by means of the potassium bromide disk technique.

Materials.—The compounds, I,[3] II,[4] 3-amino-6-chloropyridazine,[3] 3-chloro-6-hydroxypyridazine[3] and 3-chloro-6-methoxypridazine,[3] were synthesized by the known methods and purified until their physical constants gave values identical with those given in the literature.

3-Chloro-6-methylaminopyridazine (IX).—A mixture of 3.5 g. of 3,6-dichloropyridazine[5] and an aqueous solution containing 1 g. of methylamine was heated in a sealed tube at 120~130°C for 9 hr. After it had cooled, the resultant solid was collected by filtration. Recrystallization from water gave 2.3 g. of colorless needles of IX, m. p. 198~199°C. Found: N, 29.28. Calcd. for $C_5H_6ClN_3$: N, 29.27%.

A General Method for the Preparation of 3-Substituted 6-Mercaptopyridazine from 3-Substituted 6-Chloropyridazine. — A mixture of 3-substituted 6-chloropyridazine and 2 N ethanolic potassium hydrogen sulfide was heated in a sealed tube. After it had cooled, the reaction mixture was filtered to remove potassium chloride, and then the filtrate was evaporated to dryness under reduced pressure. The residue was recrystallized from a suitable solvent to obtain the product, as is shown in Table IV.

A General Method for the Preparation of 3-Substituted 6-Methylthiopyridazine from 3-Substituted 6-Chloropyridazine.—A mixture of 3-substituted 6-chloropyridazine and a 40% aqueous solution of sodium thiomethylate was heated in a sealed tube. The reaction mixture was then evaporated to dryness under reduced pressure, and the residue was recrystallized from a suitable solvent to obtain the product, as is shown in Table V.

The Methylation of I with Methyl Iodide.—a) To a solution of sodium methoxide which had been prepared from 0.3 g. of sodium and 20 ml. of methanol, 1.3 g. of 3-hydroxy-6-mercaptopyridazine (I) and 1.5 g. of methyl iodide were added. The mixture was heated in a sealed tube at 70°C for 1 hr. and then cooled and filtered to remove sodium iodide. The filtrate was evaporated to dryness, and the residue was dissolved in water and then acidified to precipitate the product. Recrystallization from water gave 1.1 g. of colorless crystals (m. p. 131.5 ~133°C, undepressed on admixture with an authentic sample of 2-hydroxy-6-methylthiopyridazine(V)). The reaction products were always the same although the molar ratios of I to methyl iodide changed from one to two.

b) When sodium hydrogen carbonate was used instead of sodium methoxide, only V was obtained, in a 63% yield.

The Methylation of I with Dimethyl Sulfate.—A mixture of 1 g. of I and 1 g. of dimethyl

5) R. H. Mizzoni and P. E. Spoerri, *J. Am. Chem. Soc.*, 73, 1873 (1951).

sulfate was heated on a steam bath for 1 hr. After the reaction mixture had been made alkaline by the addition of an aqueous solution of sodium carbonate, the solid which precipitated was collected by filtration. Recrystallization from water gave 0.8 g. of colorless crystals of V, m. p. 130~132°C. When the alkaline solution was extracted with ether, the ether extract gave 0.1 g. of colorless crystals, (m.p. 27~29°C) after evaporation.

The Methylation of II with Methyl Iodide.—a) The methylation was carried out in a sealed tube at 70°C for 1 hr. by a procedure similar to that used in the methylation of I. The product, 3-amino-6-methylthiopyridazine (XI), recrystallized from benzene, melted at 116~117°C and was not depressed on admixture with an authentic sample.

b) When sodium hydrogen carbonate was used instead of sodium methoxide, the reaction product was also only XI, in an 81% yield.

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