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## The Reaction of Phosphorus Pentasulfide with Halogen-substituted Nitrogen Heterocycles

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The novel nucleophilic displacement of halogen by sulfur, by the use of phosphorus pentasulfide in boiling pyridine has been shown to be a general reaction for activated halogen nitrogen heterocycles.

The novel nucleophilic displacement of halogen by sulfur from halogenated pyridazines was first reported by Castle and Kaji (2). Linholter (3) observed a similar displacement of halogen when he allowed 3-chloro-4-methyl-6-pyridazone to react with phosphorus pentasulfide in carbon disulfide solution to produce 4-methyl-3,6-pyridazinedithiol. Kuraishi and Castle (4) extended the scope of this reaction by allowing either 5-amino-3,4-dichloropyridazine or 4-amino-5-chloro-6-pyridazone to react with phosphorus pentasulfide in a boiling pyridine solution to obtain 5-amino-3,4-pyridazinedithiol. Malm and Castle (5) obtained imidazo[4,5-d]pyridazine-4,7-dithiol when 4,7-dichloroimidazo[4,5-d]pyridazine was treated in a similar manner. The reaction of phosphorus pentasulfide with halocinnolines was reported by Castle *et al.*, (6). Klingsberg and Papa (7) allowed either 3,5-diiodo-2-pyridone or 3,5-diiodo-4-pyridone to react with phosphorus pentasulfide in boiling pyridine solution to obtain 3,5-diiodo-2-pyridithione and 3,5-diiodo-4-pyridithione respectively. They did not obtain products in which the halogen atom had been nucleophilically displaced. This is not surprising since the 3- and 5- positions in pyridine are not generally reactive toward nucleophilic reagents. However, when R ath (8) fused 5-iodo-2-pyridone with phosphorus pentasulfide at 185 , he obtained 2-pyridithione. In this instance the halogen atom was replaced by hydrogen.

In this work either 4,5-dichloro-6-pyridazone (I) or 4,5-dibromo-6-pyridazone (III) when allowed to react with phosphorus pentasulfide in boiling pyridine solution gave 3,4,5-pyridazinetrithiol (II). The structure of II was proven by conversion into V and by the independent preparations of V via IV and VI. However when the tautomeric hydrogen atom of I was replaced by a phenyl group, the 1-phenyl-4,5-dichloro-6-pyridazone (VII) (9) when allowed to react with phosphorus pentasulfide in boiling pyridine solution gave 1-phenyl-4,5-dimercapto-6-pyridazone (VIII). It is interesting to note that the oxygen atom of VII is not replaced with sulfur. The structure of VIII was proven by conversion into IX.

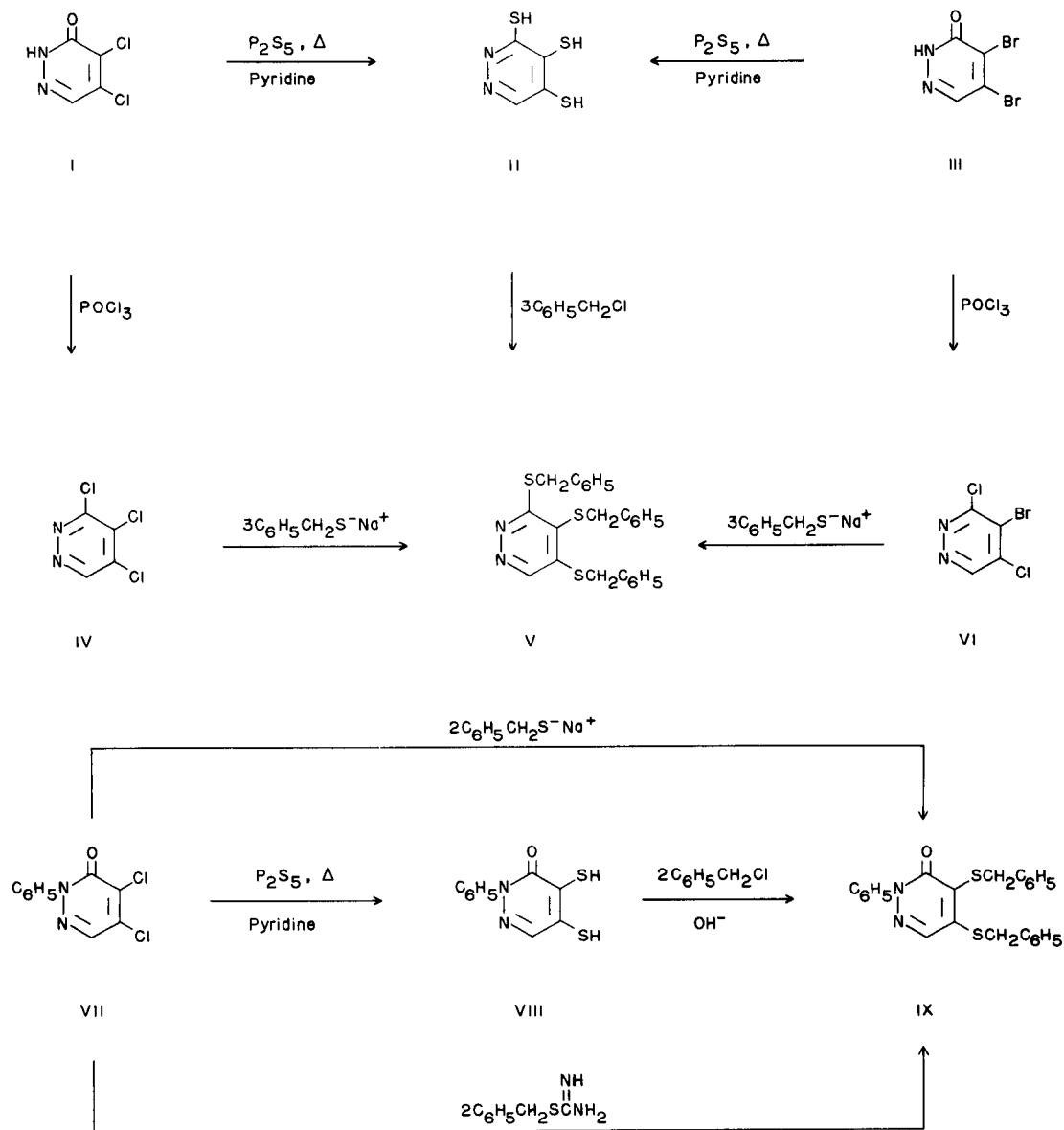
The structure of IX was verified by two independent syntheses from VII (Flow Sheet I).

3-Chloro-6-*n*-propoxy-pyridazine (X) (10) gave a 55% yield of 6-*n*-propoxy-3-pyridazinethiol (XI) by the conventional thiourea method (II) whereas a yield of 87% of XI was obtained by the phosphorus pentasulfide-pyridine method. 3,6-Dichloropyridazine (XII) (12) gave 3,6-pyridazinedithiol (XIII) (13) and 3-amino-6-chloropyridazine (XIV) (13-14) gave 3-amino-6-pyridazinethiol (XV) (15a-b) by the phosphorus pentasulfide-pyridine method. Commercial grade phosphorus pentasulfide gave a 42% yield of 6-methyl-3-pyridazinethiol (XVII) (15b-16) from 3-chloro-6-methylpyridazine (XVI) (17) whereas only a 29% yield of XVII was obtained from XVI when phosphorus pentasulfide purified by carbon disulfide extraction was used. These transformations are shown in Flow Sheet II.

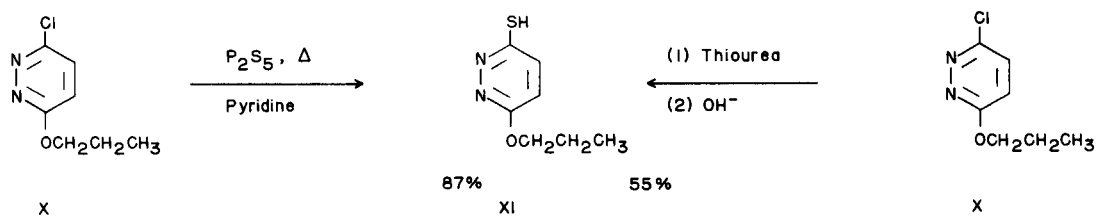
Several other halogenated nitrogen heterocycles were subjected to the phosphorus pentasulfide-pyridine reaction. Under these conditions 2-chloro-3-methylpyrazine (XVIII) (18a) gave 3-methyl-2-pyrazinethiol (XIX); 2-chloro-3,6-dimethylpyrazine (XX) (18b) gave 3,6-dichloro-2-pyrazinethiol (XXI); 2,4-dichloro-5-methylpyrimidine (XXII) (19) gave 5-methyl-2,4-pyrimidinedithiol (XXIII) (20); 2-chloro-5-nitropyridine (XXIV) (21) gave 5-nitro-2-pyridinethiol (XXV); 4-chlorocinnoline (XXVI) (22) gave 4-cinnolinethiol (XXVII) (23); 1-chlorophthalazine (XXVIII) (24) gave 1-phthalazinethiol (XXIX) (25); 4-chloroquinazoline (XXX) (26) gave 4-quinazolinethiol (XXXI) (27); and 2-chloroquinoline (XXXII) (28) gave 2-quinolinethiol (XXXIII) (29). These transformations are shown in Flow Sheet III.

The above examples establish the generality of the novel nucleophilic displacement of halogen from reactive positions in nitrogen heterocycles. In order to ascertain whether this reaction could be extended to activated halobenzenes, 2,4-dinitrochlorobenzene (XXXIV) was allowed to react with phosphorus pentasulfide in boiling pyridine solution. A 36% yield of 2,4-dinitrothiophenol (XXXV) (30) was obtained. Furthermore when XXXIV was allowed to react with phosphorus pentasulfide in boiling toluene solution a 74% yield of XXXV was obtained.

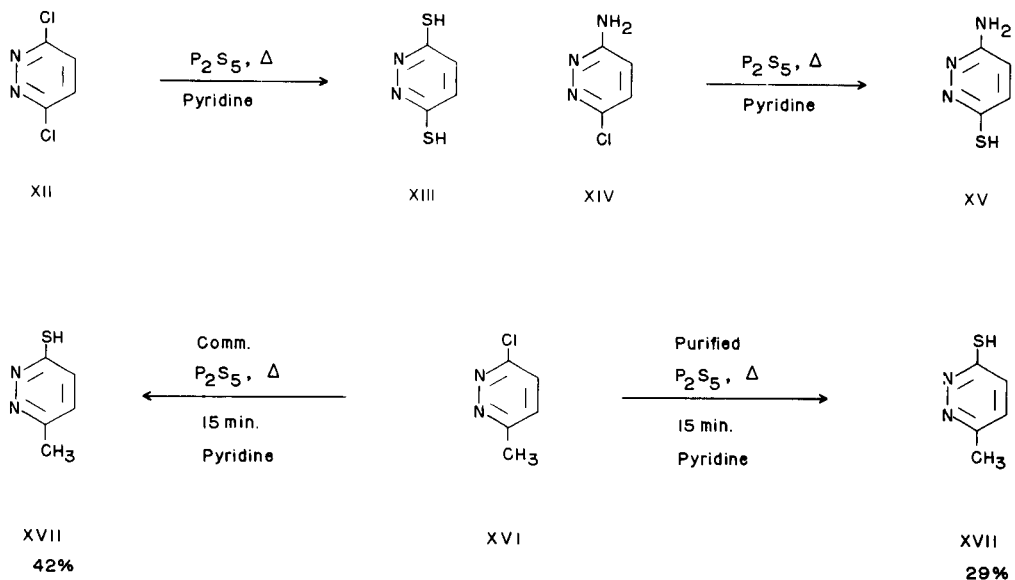
## FLOW SHEET I



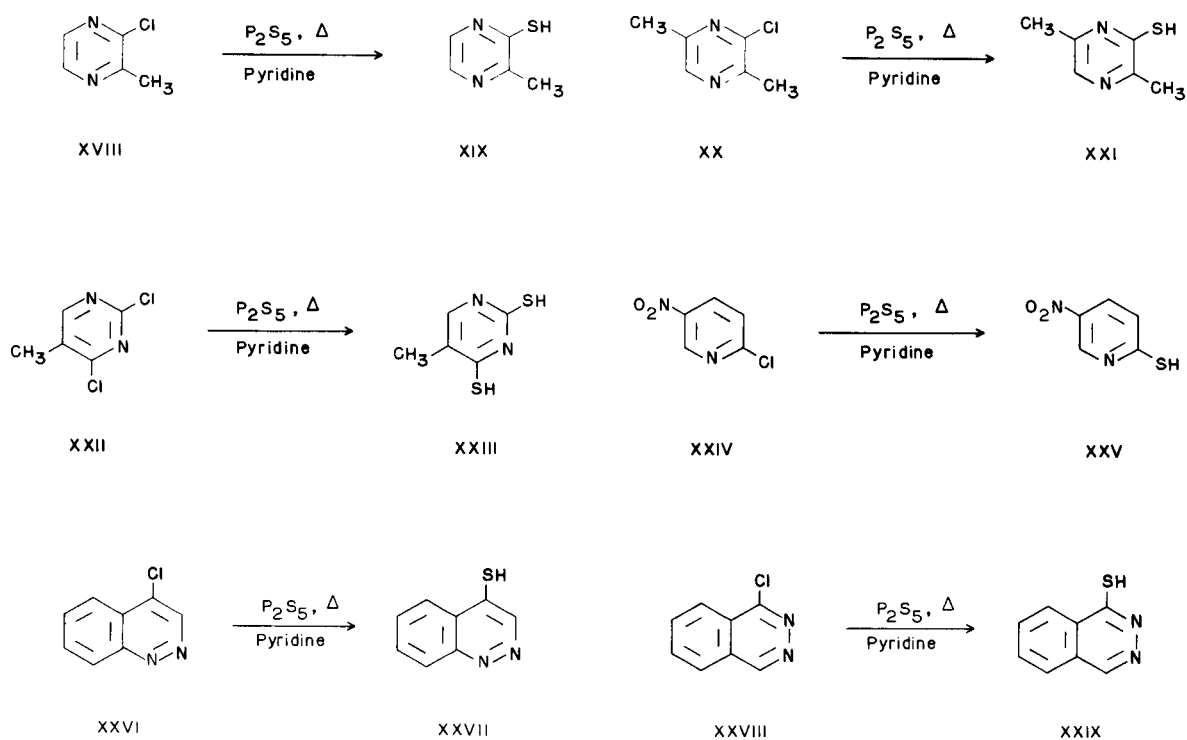
## FLOW SHEET II



FLOW SHEET II CONTINUED



FLOW SHEET III



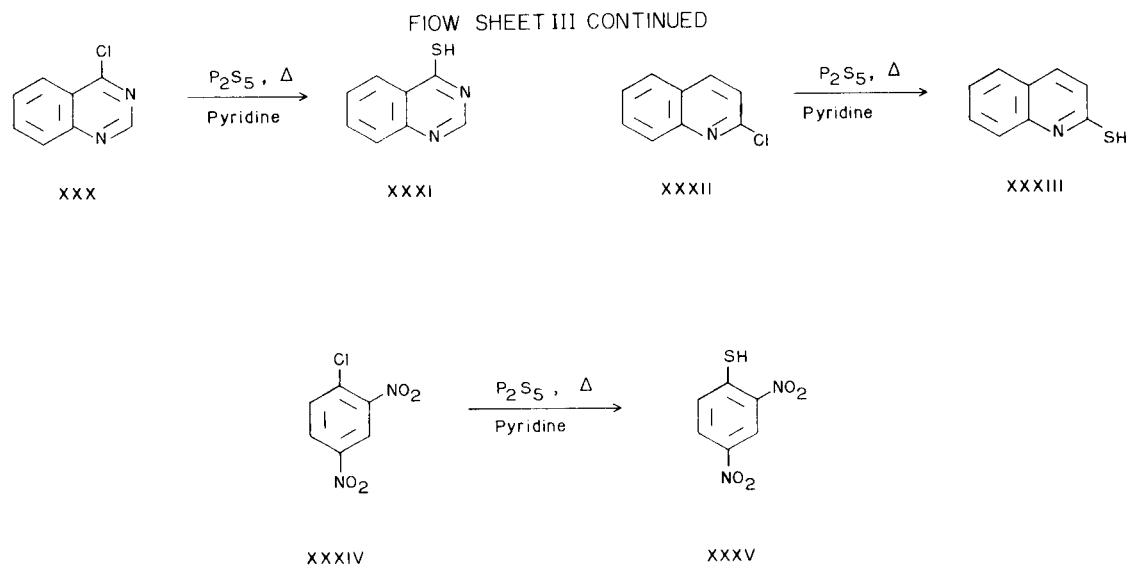


TABLE I (a)

Compounds Obtained From the Nucleophilic Displacement Reaction

No. of Product	Product	Reactant	M. p. °C of Product	Reaction Solvent	Purification Solvent	Literature Reference	Yield, %
II	3,4,5-Pyridazine-trithiol (b)	4,5-Dichloro- or 4,5-Dibromo-6-pyridazine	>400	Pyridine	(b)	(2)	(b)
VIII	1-Phenyl-4,5-dimercapto-6-pyridazine (c)	4,5-Dichloro-1-phenyl-6-pyridazine	110	Pyridine	Benzene-cyclohexane	(2)	78
XI	6- <i>n</i> -Propoxy-3-pyridazinethiol	3-Chloro-6- <i>n</i> -propoxy-pyridazine	159-161	Pyridine	Ethanol	(11)	87
XIII	3,6-Pyridazine-dithiol	3,6-Dichloro-pyridazine	245-246 dec.	Pyridine	Methanol	(13) (d)	~50
XV	3-Amino-6-pyridazinethiol	3-Amino-6-chloro-pyridazine	281-282	Pyridine	(e)	(15) (e)	18
XVII	6-Methyl-3-pyridazinethiol	3-Chloro-6-methylpyridazine	205-209 dec.	Pyridine	Ethanol	(16) (f)	(f)
XIX	3-Methyl-2-pyrazinethiol	3-Methyl-2-chloropyrazine	210-214 dec.	Pyridine	Benzene-Ethanol	(g)	95
XXI	3,6-Dimethyl-2-pyrazinethiol	2-Chloro-3,6-dimethylpyrazine	224-225 dec.	Pyridine	Benzene-Ethanol	(h)	~90
XXIII	5-Methylpyrimidine-2,4-dithiol	2,4-Dichloro-5-methylpyrimidine	284-285	Pyridine	Aqueous Ethanol	(20a-b)	~65
XXV	5-Nitro-2-pyridinethiol	2-Chloro-5-nitropyridine	175-177 dec.	Pyridine or Toluene	Methanol	(i)	50-80
XXVII	4-Cinnolinethiol	4-Chlorocinnoline	204-205	Pyridine	(j)	(23)	70
XXIX	1-Phthalazinethiol	1-Chlorophthalazine	178-179	Pyridine	Benzene	(25) (k)	75
XXXI	4-Quinazolinethiol	4-Chloroquinazoline	314-315	Pyridine	Methanol	(27)	85
XXXIII	2-Quinolinethiol	2-Chloroquinoline	175-177	Pyridine	Ethanol	(29)	55
XXXV	2,4-Dinitrothiophenol	2,4-Dinitrochlorobenzene	129-130	Pyridine or Toluene	Ligroin	(30) (l)	36-74 (m)

(a) Molecular formulas and analytical data are recorded in the footnotes. (b) This compound was insoluble in every solvent tried. It was purified by dissolving in dilute sodium hydroxide solution and precipitation with dilute hydrochloric acid solution to pH 1-1.5. The final product was washed with water and ethanol. The yield from I was 76% and from III was 89%. *Anal.* Calcd. for  $C_4H_4N_2S_3$ : C, 27.25; H, 2.29; N, 15.89. Found: C, 27.37; H, 2.05; N, 15.77. (c) *Anal.* Calcd. for  $C_{10}H_8N_2OS_2$ : C, 50.82; H, 3.41; N, 11.86. Found: C, 50.33; H, 3.15; N, 11.47. (d) Lit. (13) m.p. 230-240° dec. (e) Lit. (15a) m.p. 250° dec.; Lit. (15b) m.p. 215-217° dec. Compound XV was purified by precipitation from basic solution with acid. Attempts to recrystallize XV from methanol were not successful, however the methanol-digested product was used for the analytical sample. *Anal.* Calcd. for  $C_4H_5N_3S$ : C, 37.78; H, 3.96; N, 33.04; S, 25.22. Found: C, 37.93; H, 4.39; N, 33.44; S, 24.76. (f) Lit. (15b) m.p. 203°; Lit. (16) m.p. 203.5-205°. The use of purified phosphorus pentasulfide gave a yield of 29% of XVII while commercial grade phosphorus pentasulfide gave a yield of 42% of XVII after just 15 minutes reaction time. (g) *Anal.* Calcd. for  $C_5H_5N_2S$ : C, 47.61; H, 4.80; N, 22.22. Found: C, 47.83; H, 4.94; N, 21.89. (h) *Anal.* Calcd. for  $C_6H_6ClN_2S$ : C, 40.79; H, 5.14; N, 15.86. Found: C, 41.33; H, 5.33; N, 16.14. (i) *Anal.* Calcd. for  $C_5H_4N_2OS_2$ : C, 38.46; H, 2.58; N, 17.94. Found: C, 38.53; H, 2.77; N, 18.08. (j) The compound was purified by repeated precipitation with dilute hydrochloric acid from an alkaline solution. It was finally washed with water and ethanol. (k) Lit. (25) m.p. 170-171°. (l) Lit. (30) m.p. 131°. (m) The yields are reported after three recrystallizations.

## EXPERIMENTAL (31)

The nucleophilic displacement of halogen with phosphorus pentasulfide in pyridine is illustrated by the procedure for the preparation of 4-cinnolinethiol.

4-Chlorocinnoline (0.5 g., 0.003 mole), phosphorus pentasulfide (2.13 g., 0.013 mole) and 30 ml. of pyridine (dried over potassium hydroxide) were heated under reflux for one hour. The pyridine was removed by evaporation under reduced pressure and the pasty residue was hydrolyzed by the addition of ice followed by heating the mixture on the steam bath in the hood for 2 hours until the evolution of hydrogen sulfide had ceased. The solution was filtered hot and the red precipitate was collected. An additional amount of red crystals was collected after the filtrate was allowed to cool. The filtrate was acidified to pH 1 after removing the second crop of red crystals, however no additional solid was obtained (32). The combined red crystalline solids melted over a range of 184-190°. The combined solids were dissolved in 1 N sodium hydroxide solution, heated with charcoal, the charcoal removed by filtration and the filtrate acidified to pH 1-2 with 1 N hydrochloric acid solution and allowed to cool. Bright orange fluffy needles which were washed with water were obtained, m.p. 204-205°; yield 0.35 g. (70%). A mixture melting point of this compound and 4-cinnolinethiol (23) showed no depression.

The novel nucleophilic displacement of halogen with phosphorus pentasulfide in toluene solution is illustrated below.

2,4-Dinitrochlorobenzene (2.0 g., 0.01 mole), phosphorus pentasulfide (3.8 g., 0.024 mole) and 35 ml. of dry toluene were heated under reflux for 4 hours. The toluene was removed by distillation and the residual yellow paste hydrolyzed with 200 g. of an ice-water mixture. This was followed by heating the mixture on the steam bath in the hood for 6 hours until the evolution of hydrogen sulfide had ceased. The yellow solid remaining was removed by filtration. It amounted to 0.5 g. The filtrate was acidified to pH 1-1.5 with 1 N hydrochloric acid solution and allowed to stand overnight. An additional amount of product (1.4 g.) was collected. The combined crude yield amounted to 1.9 g. (95%). The product was recrystallized from benzene, followed by two recrystallizations from ligroin. The total yield of pure product, m.p. 129-130° (lit. (30) m.p. 131°) was 1.48 g. (74%).

## 3,4,5-(Trisbenzylthio)pyridazine (V).

Benzyl chloride (5.06 g., 0.04 mole) was added to 0.88 g. (0.005 mole) of II in a mixture of 40 ml. of 5% aqueous sodium hydroxide solution, 30 ml. of 28% aqueous ammonia and 40 ml. of ethanol with stirring at room temperature. The mixture was stirred overnight. The solid which separated was collected by filtration, washed with a small amount of ethanol and water and dried. It was purified by recrystallization from benzene-cyclohexane to give 1.90 g. (85%) of V, colorless needles, m.p. 151-152°. The analytical sample was recrystallized from cyclohexane, m.p. 157°.

*Anal.* Calcd. for  $C_{26}H_{22}N_2S_3$ : C, 67.22; H, 4.97; N, 6.27. Found: C, 66.89; H, 4.62; N, 6.38.

## The Reaction of 4,5-Dibromo-6-pyridazine with Phosphorus Oxychloride.

4,5-Dibromo-6-pyridazine (III) (25.4 g., 0.1 mole) was added to 150 ml. of phosphorus oxychloride and the mixture was heated for 4.5 hours. The excess phosphorus oxychloride was removed under reduced pressure. The residue was poured onto crushed ice and the residue was extracted with ether. The ethereal extract was washed with water, then with dilute sodium carbonate and finally with water. The ether layer was dried (anhydrous magnesium sulfate), the ether was evaporated and the residue was distilled under reduced pressure to give 17.7 g. of product, m.p. ~70°. Upon recrystallization from petroleum ether, colorless needles, m.p. 86°, were obtained.

The analytical data suggested that the product was predominantly 4-bromo-3,5-dichloropyridazine. It could be 5-bromo-3,4-dichloropyridazine, but this is unlikely since it would be expected that exchange would take place at the more unhindered 5-position.

*Anal.* Calcd. for  $C_4H_2BrCl_2N_2$ : C, 20.98; H, 0.88. Found: C, 21.73; H, 0.56.

## 4,5-Bis(benzylthio)-1-phenyl-6-pyridazine (IX).

4,5-Dichloro-1-phenyl-6-pyridazine (VII) (1.20 g., 0.005 mole) in 60 ml. of ethanol was added to benzyl isothiuronium hydrochloride (2.02 g., 0.01 mole) dissolved in 40 ml. of 5% aqueous sodium hy-

droxide solution. The mixture was stirred overnight at room temperature. The solid product was separated by filtration, washed with water and dried. There was obtained 2.08 g. (quantitative yield) of product, m.p. 157°. The compound was purified by recrystallization from benzene-cyclohexane to give pale yellow crystals, m.p. 163°, which showed no depression in melting point when mixed with the samples previously prepared by the two other methods described by Castle and Kaji (11).

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- (31) All melting points were taken in capillary tubes either in a heated copper block or in a Thomas-Hoover melting point apparatus and are uncorrected.
- (32) In some instances it was necessary to acidify the original filtrate in order to obtain the mercapto heterocycles. This obviously depends upon the solubility of the mercapto heterocycle in the filtered hydrolysis solution.

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