S-Demethylation of Nitrogen Heterocycles (1a)

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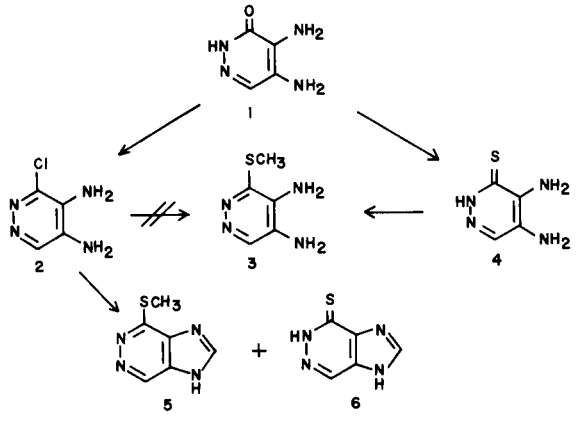
Received August 4, 1980

When 3-chloro-4,5-diaminopyridazine (**2**) was treated with sodium methylmercaptide in refluxing *N,N*-dimethylformamide, two heterocycles were formed and isolated, neither of which was the expected 3-methylthio-4,5-diaminopyridazine (**3**). A thorough spectral analysis of these heterocycles showed them to be 4-methylthioimidazo[4,5-*d*]pyridazine (**5**) and imidazo[4,5-*d*]pyridazine-4-thione (**6**). *N,N*-Dimethylformamide was found to provide the one carbon unit required for the formation of **5**. The origin of **6** was shown to be a result of *S*-demethylation of **5**. *S*-Demethylation of **3** could also be effected with sodium methylmercaptide in methyl sulfoxide without the occurrence of annulation. In methyl sulfoxide the process of demethylation was accelerated and occurred at lower temperature.

J. Heterocyclic Chem., **18**, 303 (1981).

Certain 4-substituted imidazo- and *v*-triazolo[4,5-*d*]pyridazines can act as substrates (2) or inhibitors (3,4) of salvage pathway enzymes and therefore have the potential to function as chemotherapeutic agents. One approach to their synthesis involves ring closure of 3-methylthio-4,5-diaminopyridazine (**3**) (5) followed by nucleophilic displacement of the methylthio group (6). 3-Methylthio-4,5-diaminopyridazine (**3**) had been prepared (7) by methylation of 4,5-diaminopyridazine-3-thione (**4**). The thione **4**, in turn, was synthesized from 4,5-diaminopyridazine-3-one (**1**) in the presence of phosphorus pentasulfide (P_2S_5) and pyridine at reflux (7). Attempts at scaling up this reaction according to the published procedure met with failure and therefore we turned our attention to an alternate route to **3** *via* 3-chloro-4,5-diaminopyridazine (**2**). This heterocycle had been isolated (7) as a minor product in the catalytic reduction of 4,5-diamino-3,6-dichloropyridazine. Since **2** was desired in large quantities, it was prepared directly from **1**. Treatment of **1** with phosphorus oxychloride ($POCl_3$) and a catalytic amount of *N,N*-dimethylaniline furnished **2** in good yield.

Conversion of chloroazines to their corresponding methylthio analogs with sodium methylmercaptide has been accomplished in various solvents (8). Our initial solvent choice was ethanol, but under the conditions employed, *i.e.*, either at reflux or at 100° in a steel reaction vessel, **2** remained unchanged. We then replaced ethanol with *N,N*-dimethylformamide (8c,9a) (DMF) and a reaction of **2** with sodium methylmercaptide occurred (tlc). After work-up of the reaction mixture, a ^{1}H nmr (DMSO-d_6) spectrum was obtained on the crude solid. Five signals were observed in the spectrum at δ 2.83, 8.63, 8.66, 8.92, and 9.50. The high field signal at δ 2.83 was assigned to the SCH_3 function. The four low field resonances were sharp singlets that did not exchange on addition of deuterium oxide. This was indeed different from the ^{1}H nmr spectrum of **3** which exhibited resonances at δ 2.57 (SCH_3), 5.17 and 5.57 (NH_2; exchangeable), and 8.18 (H6). Although tlc suggested a single component, the aforementioned spectral data indicated we had a mixture which did not contain the desired **3**. On the basis of this spectral evidence, the material was subjected to a high pressure liquid chromatographic (hplc) analysis. The material contained two components in a 11:1 ratio neither of which was **3**. The two components were then separated by column chromatography and a rigorous spectral and chemical study was undertaken to determine their structures. The results of these studies indicated that the major component was 4-methylthioimidazo[4,5-*d*]pyridazine (**5**) and the minor component was imidazo[4,5-*d*]pyridazine-4-thione (**6**) (Scheme 1).



Scheme 1

Having determined the structures of the two components as **5** and **6**, two questions remained unanswered: 1) how did ring closure occur and 2) what was the origin of **6**. We felt that DMF played a role in the ring closure of these heterocycles and a perusal of the literature confirmed our suspicions. Mercaptide ion (10) or sulfur (S_8) (11) catalyzed ring closures in DMF have been reported and are believed to occur by means of an active "thiocarbonyl intermediate" generated (Scheme 2) by the liberation of dimethylamine from a reaction intermediate or from DMF *per se* (12). Undoubtedly, a similar action by methylmercaptide ion on such an intermediate is occurring in our

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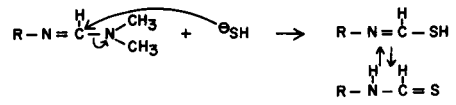

Scheme 2

reaction sequence and provides the one-carbon unit (C2) for annulation to the imidazole moiety.

We now turned our attention to the origin of **6**. We envisaged three possible pathways for the formation of **5** and **6** as illustrated in Figure 1. The first pathway, pathway A,

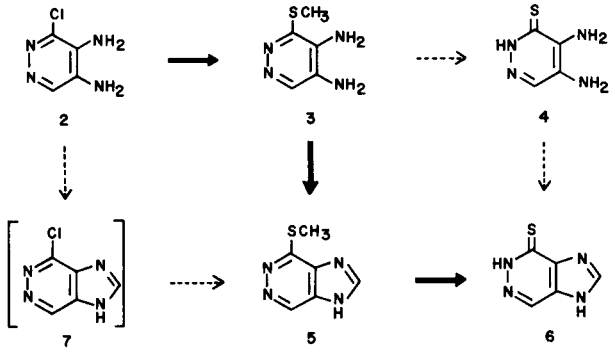

Figure 1. The proposed pathways leading to 4-methylthioimidazo[4,5-*d*]-pyridazine (**5**) and imidazo[4,5-*d*]pyridazine-4-thione (**6**) are as follows: Pathway A, **2** → **7** → **5** → **6**; Pathway B, **2** → **3** → **5** → **6**; and Pathway C, **2** → **3** → **4** → **6** and **3** → **5**.

involves ring closure to 4-chloroimidazo[4,5-*d*]pyridazine (**7**) followed by nucleophilic displacement of the chloro group to give **5**. The heterocycle **5** then undergoes *S*-demethylation to furnish imidazo[4,5-*d*]pyridazine-4-thione (**6**). The second route, pathway B, involves displacement of the chloro group on **2** by methylmercaptide ion to afford **3**. Annulation of **3** would provide **5** and *S*-demethylation of this heterocycle would give rise to **6**. The third pathway, pathway C, involves initial conversion of **2** to **3** as in pathway B. This ring-opened heterocycle (**3**) could then undergo either *S*-demethylation or ring closure to furnish **4** or **5**, respectively. The intermediate **4** could then ring close to provide **6**. To test this hypothesis, the proposed intermediates **3**, **4**, and **5** were synthesized by unambiguous routes and subjected to the original reaction conditions, *i.e.*, a three to fourfold excess of methylmercaptide ion in DMF at reflux for 17 hours. In addition to these three heterocycles, the reaction of **2** was reexamined. Each reaction was monitored by tlc and after removal of the solvent the crude reaction mixture was carefully analyzed by high pressure liquid chromatography. The results are shown in Table I. These data allow one to differentiate between the three proposed pathways and definitely supports pathway B. Reexamination of the reaction of 3-chloro-4,5-diaminopyridazine (**2**), even at selected time intervals, indicated that only 4-methylthioimidazo[4,5-*d*]pyridazine (**5**) and imidazo[4,5-*d*]pyridazine-4-thione (**6**) were formed. No other heterocycles were detected (13). The reaction of **3** was complete within 3 hours and afforded exclusively **5** and **6** with **5** predominating. The fact that **4** was not detected suggests that under these reaction conditions ring closure is preferred to *S*-demethylation and rules out the formation of **6** *via* pathway C. This is further supported by the sluggish manner in which **4** was converted to **6**. If 4,5-diaminopyridazine-3-thione (**4**) was the precursor of imidazo[4,5-*d*]pyridazine-4-thione (**6**), it should have been detected. Although our data overwhelmingly favors pathway B (solid arrows), pathway A cannot be ignored. However, efforts to synthesize 4-chloroimidazo[4,5-*d*]-

Table I

Reaction of Certain 3-Substituted-4,5-diaminopyridazines and 4-Methylthioimidazo[4,5-*d*]pyridazine with Sodium Methylmercaptide in *N,N*-Dimethylformamide at Reflux (a).

Starting Heterocycle	Reaction Time (Hours)	Reaction Products (b)	Retention time (c) (Minutes)	% Products (d)
2	17 (e)	**5**	5.3	91.7
		6	2.9	8.3
3	3	**5**	5.3	95.2
		6	2.9	4.8
4	17	**4**	2.4	41.8
		6	2.9	58.2
5	17	**5**	5.3	76.3
		6	2.9	23.7

(a) High pressure liquid chromatography was used to identify and determine the amount of crude materials in the reaction mixture. The hplc analyses were conducted on a Waters ALC 202 Liquid Chromatography equipped with a Model 444 Absorbance Detector. The detection wavelength used was 254 nm. Integration of the peak areas was performed electronically using a Hewlett-Packard Model 3380-A Integrator. A Partisil C_{18} reverse phase column was employed and the solvent system used was methanol-*p*H 5.6 phosphate buffer (26:76, V/V). The flow rate was 1.5 ml./minute. Approximately 1 mg. of each mixture was dissolved in 1 ml. of distilled water and 3-5 μl. was injected. After every hplc analysis, each mixture was co-injected with an authentic sample to corroborate peak identification. (b) With **4** and **5** the reactions were incomplete and these starting heterocycles were isolated in the crude mixture. (c) The retention times for authentic samples are as follows: **2** (3.1 minutes), **3** (3.8 minutes), **4** (2.4 minutes), **5** (5.3 minutes), and **6** (2.9 minutes). (d) All data were reproducible. (e) The reaction of **2** was examined after 3 hours and 10 hours. Unreacted **2**, **5** and **6** were the only heterocycles detected.

pyridazine (7) from imidazo[4,5-*d*]pyridazine-4-one in our laboratory as well as in others (6) have failed. Furthermore, attempted ring closure of **2** even under the mildest conditions, *e.g.*, diethoxymethyl acetate, either gave a ring opened intermediate or imidazo[4,5-*d*]pyridazine-4-one. Since we did not detect (13) the formation of any other heterocycles when **2** was subjected to the methylmercaptide/DMF reaction, we feel certain that the formation of **5** from **7** (pathway A) is highly improbable.

Sodium ethylmercaptide in refluxing DMF has been employed (15) to demethylate aryl methyl ethers. The ethylmercaptide ion cleaves the methyl carbon-oxygen (O-CH_3) bond to provide the desired phenol. Support for this mechanism has been provided by the isolation of ethyl methyl sulfide. A similar mechanism is most likely occurring in our case. Methylmercaptide ion cleaves the methyl carbon-sulfur bond (S-CH_3) providing the respective thioheterocycles (16).

We were interested in the potential utility of the *S*-demethylation reaction as an alternate route to thioheterocycles. Thus, we sought an appropriate solvent which would avoid the possibility of ring closure. We selected methyl sulfoxide (Me_2SO). Treatment of either **3** or **5** with sodium methylmercaptide in methyl sulfoxide at 120° afforded their respective *S*-demethylated products in moderate yields. Methyl sulfoxide has been employed in the oxidation of thiols to disulfide (17), however, in neither case did we find any evidence of disulfide formation. In addition, we did not observe any oxidation of **3** or **5** to their corresponding oxygen analogs (18). It is worth mentioning that 6-methylthiopurine was resistant to demethylation when either solvent was employed.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. The infrared spectra were determined in pressed potassium bromide disks with a Beckman IR-8 Spectrophotometer. The ^{1}H nmr spectra were determined on a Varian A-60 or Varian EM-360A 60 MHz Spectrometer. Chemical shifts are expressed in parts per million with respect to TMS; s = singlet, d = doublet, vbs = very broad singlet. The ultraviolet absorption spectra were recorded on a Beckman DB-GT Grating Spectrophotometer. High pressure liquid chromatography was conducted on a Waters ALC 202 Liquid Chromatograph equipped with a Model 444 Absorbance Detector and the methods used are described in Table I. Thin layer chromatography was run on precoated (0.25 mm) Silica Gel 60 F-254 plates manufactured by EM Laboratories, Inc. and short wave ultraviolet light (254 nm) was used to detect the uv absorbing spots. EM Kieselguhr suitable for column chromatography was used in the pre-columns and EM Silica Gel 60 (70-230 mesh ASTM) was employed for routine column chromatography. All solvent proportions were by volume. Evaporations were performed with a Buchi Rotovapor at 40° unless otherwise stated. Elemental analyses were performed by M-H-W Laboratories, Phoenix, Arizona.

The following heterocycles employed to prepare the desired authentic 3-substituted-4,5-diaminopyridazines and 4-substituted imidazo[4,5-*d*]-pyridazines are listed below along with their melting points and pertinent spectral data. Although the synthesis of the parent pyridazone, 4,5-dichloropyridazine-3-one, has been described by treatment of mucochloric acid with either semicarbazide hydrochloride (19a), hydrazine hydrate (19b), or hydrazine sulfate (19c) in alcohols (ethanol and butanol), acetic acid, or aqueous media, we have included our experimental procedure using 95% hydrazine in absolute ethanol. This simple, one-pot reaction eliminates the azeotropic distillation of water required by several preparations. In addition, a new large-scale procedure for 4,5-diaminopyridazine-3-thione (**4**) is provided. The synthesis of 4,5-diamino-3-methylthiopyridazine (**3**) has also been included, since the published procedure (7), which calls for a 60% excess of methyl iodide, affords 4,5-diamino-1-methyl-3-methylthiopyridazinium iodide (20) as the major product instead of the desired **3**.

4,5-Dichloropyridazine-3-one.

To a three-necked, round bottom flask (3 liter), fitted with a condenser and dropping funnel, was added mucochloric acid (200 g., 1.19 moles) (Aldrich) and absolute ethanol (1 liter). The resulting solution was mechanically stirred and cooled to 5°. To this solution was added 95% hydrazine (38 g., 1.19 moles) (Eastman) dropwise, while carefully maintaining the temperature at 5°. When one-half of the amount of hydrazine had been added, an orange-yellow crystalline precipitate formed. After the addition of hydrazine was complete, the reaction mixture was heated at reflux for 6 hours. The initial precipitate dissolved upon heating, and after a short period of time the product began to precipitate as yellowish crystals. The mixture was then allowed to cool to room temperature and the crystalline material was collected by filtration. This material was recrystallized from 95% ethanol to provide 4,5-dichloropyridazine-3-one (178.9 g., 91%) as needles, m.p. 199.5-200° [lit. (17a) 202°, (19c) 199-200°]; ^{1}H nmr (DMSO-d_6): δ 8.00 (s, 1, H6), 13.5 (vbs, 1, NH); uv (ε x 10^{-3}) λ max (*p*H 1): 290 nm (4.03); λ min (*p*H 1): 258 nm (1.72); λ max (water): 290 nm (4.08); λ min (water): 258 nm (1.86); λ max (*p*H 11): 306 nm (4.26), sh 242 (3.63), 224 (11.05); λ min (*p*H 11): 262 nm (0.36) [lit. (19b); λ max (ethanol): 298 nm (3.89); λ max (NaOH): 306 nm (4.57)].

4,5-Diaminopyridazine-3-one (**1**).

This compound was prepared by the method of Reicheneder and Dury (21). The reduction was carried out with Raney Nickel No. 30 (22); m.p. 231-232° [lit. (21) 224-225°]; ^{1}H nmr (DMSO-d_6): δ 4.85 (bs, 2, NH_2), 5.25 (bs, 2, NH_2), 7.32 (s, 1, H6), 12.07 (vbs, 1, NH); uv (ε x 10^{-3}) λ max (*p*H 1): sh 318.5 nm (2.90), sh 304 (3.91), sh 293 (4.41), 272 (5.30); λ min (*p*H 1): 243 nm (2.22); λ max (water): 304 nm (7.69), sh 276 (4.74), 225.5 (21.24); λ min (water): 247 nm (2.02); λ max (*p*H 11): 303.5 nm (7.44), sh 276.5 (4.88), 228 (18.87); λ min (*p*H 11): 247 nm (2.27).

3-Chloro-4,5-diaminopyridazine (**2**).

4,5-Diaminopyridazine-3-one (**1**) (2 g., 15.9 mmoles) was added to solution containing phosphorus oxychloride (40 ml.) and *N,N*-dimethylaniline (4 ml.). The reaction mixture was heated at reflux with stirring for 10 hours and then allowed to cool to room temperature. The excess phosphorus oxychloride was removed under diminished pressure and then cracked ice was carefully added to the viscous residue while maintaining the temperature below 10°. The resulting solution was neutralized to *p*H 7 (*p*H meter) with a 30% sodium carbonate solution and then extracted with ethyl ether (3 x 50 ml.) to remove the last traces of *N,N*-dimethylaniline. The aqueous layer was then evaporated to dryness using a moderate stream of air. The air-dried residue was extracted with AR methanol (*ca.* 5 x 100 ml.) until the methanol layer was no longer uv positive (tlc). The methanol washings were combined and evaporated to dryness under diminished pressure. The residue was then placed in a Soxhlet extraction apparatus and extracted with ethyl acetate for 72 hours. The crystalline solid obtained by this process was recrystallized from AR methanol to provide 1.1 g. (50%) of **2** as cubical crystals, m.p. 197-198° dec. [lit. (7) 207-208 dec.]; ^{1}H nmr (DMSO-d_6): δ 5.62 (s, 2, NH_2), 5.83 (s, 2, NH_2), 8.15 (s, 1, H6); uv (ε x 10^{-3}) λ max (*p*H 1): 326 nm (8.62), 291 (5.72), 228.5 (19.86); λ min (*p*H 1): 298 nm (5.70), 248 (0.88); λ max (water): 290 nm (8.76), 221.5 (22.78); λ min (water): 245 nm (2.04); λ max (*p*H 11): 290 nm (9.00), 226.5 (16.02); λ min (*p*H 11): 243 nm (2.15).

Anal. Calcd. for $C_4H_5ClN_4$: C, 33.23; H, 3.49; N, 38.76; Cl, 24.52.

Found: C, 32.96; H, 3.73; N, 38.53; Cl, 24.36.

4,5-Diaminopyridazine-3-thione (**4**).

Purified phosphorus pentasulfide (23) (6.66 g., 30 mmoles) was added to a solution of **1** (2.52 g., 20 mmoles) in β-picoline (200 ml.) and the mixture was heated at reflux for 4 hours. After cooling, the excess solvent was removed under diminished pressure to provide a syrupy residue. Ice water (60 ml.) was added to the residue, the resulting suspension was allowed to warm to room temperature, and then the suspension was heated on a steam bath for 2 hours. While the suspension was still hot, a 10% sodium hydroxide solution was added dropwise to effect solution of the solid material. The hot solution was treated with Norit and filtered through a Celite bed. The cooled filtrate was acidified to *p*H 1 with concentrated hydrochloric acid and refrigerated (4°) overnight. The precipitated solid was removed by filtration and recrystallized from 95% ethanol to furnish 2.64 g. (93%) of **4**, m.p. 275-276° [lit. (7) 241-243°]; ^{1}H nmr (DMSO-d_6): δ 5.70 (bs, 2, NH_2), 5.97 (bs, 2, NH_2), 7.83 (s, 1, H6); uv (ε x 10^{-3}) λ max (*p*H 1): 342.5 nm (8.87), 264 (13.06), 243 (11.75); λ min (*p*H 1): 285 nm (2.79), 252 (10.70), 225.5 (6.55); λ max (water): 342 nm (9.29), 263.5 (12.39), 242.5 (11.94); λ min (water): 285 nm (2.25), 252 (10.32), 225 (6.33); λ max (*p*H 11): 310 nm (2.58), 249 (9.43); λ min (*p*H 11): 283 nm (1.86), 223 (2.25).

3-Methylthio-4,5-diaminopyridazine (**3**).

4,5-Diaminopyridazine-3-thione (**4**) (14.52 g., 0.102 mole) was dissolved in 0.5 *N* potassium hydroxide (204 ml., 0.102 equivalent) and to this solution was added methyl iodide (14.50 g., 6.36 ml., 0.102 mole). The mixture was stirred at room temperature for 20 hours and the solid that formed was collected by filtration. Recrystallization from 95% ethanol afforded 11 g. (75%) of **3** as yellow granules, m.p. 195-196° [lit. (7) 193.5-194.5°]; ^{1}H nmr (DMSO-d_6): δ 2.57 (s, 3, SCH_3), 5.17 (bs, 2, NH_2), 5.57 (bs, 2, NH_2), 8.18 (s, 1, H6); uv (ε x 10^{-3}) λ max (*p*H 1): 331.5 nm (8.62), sh 299.5 (5.97), 257.5 (14.06); λ min (*p*H 1): 277 nm (3.25), 238 (9.50); λ max (water): sh 339.5 (3.06), 300 (7.19), sh 259.5 (8.44), 241.5 (13.47); λ min (water): 272.5 (4.34); λ max (*p*H 11): 296.5 nm (8.12), 242 (16.34); λ min (*p*H 11): 266.5 nm (4.92).

4-Methylthioimidazo[4,5-*d*]pyridazine (**5**).

This compound was prepared according to Martin and Castle (6), m.p. 242° [lit. (6) 235-236°]; ^{1}H nmr (DMSO-d_6): δ 2.87 (s, 3, SCH_3), 8.82 (s, 1, H2), 9.63 (s, 1, H7), 13.09 (vbs, 1, NH); uv (ε x 10^{-3}) λ max (*p*H 1): sh 300 nm (4.92), 277 (7.56), 237.5 (11.57); λ min (*p*H 1): 256.5 nm (3.82), 220 (7.15); λ max (water): 272.5 nm (8.16), 223 (13.05); λ min (water): 243.5 nm (3.84); λ max (*p*H 11): sh 289.5 nm (5.07), 277 (7.43), 230.5 (15.17); λ min (*p*H 11): 255.5 nm (4.90).

Imidazo[4,5-*d*]pyridazine-4-thione (**6**).

This heterocycle was prepared according to Martin and Castle (6), m.p. >300° [lit. (6) >300°]; ^{1}H nmr (DMSO-d_6): δ 8.76 (s, 1, H2), 9.05 (s, 1, H7), 14.30 (vbs, 1, NH), 14.70 (vbs, 1, NH); uv (ε x 10^{-3}) λ max (*p*H 1): 312.5 nm (12.47), sh 246.5 (5.27), 226.5 (10.92); λ min (*p*H 1): 256 nm (0.94); λ max (water): 311.5 nm (12.52), sh 247.5 (6.71), 231 (11.13); λ min (water): 258.5 nm (1.22); λ max (*p*H 11): 309 nm (15.01), 246 (12.40); λ min (*p*H 11): 266 nm (2.28).

Reaction of 3-Chloro-4,5-diaminopyridazine (**2**) with Sodium Methylmercaptide in *N,N*-Diamethylformamide.

A. Isolation and Identification of 4-Methylthioimidazo[4,5-*d*]pyridazine (**5**) and Imidazo[4,5-*d*]pyridazine-4-thione (**6**).

To a suspension of sodium methylmercaptide (24) (500 mg., 7.1 mmoles) in dry *N,N*-dimethylformamide (10 ml.) was added 3-chloro-4,5-diaminopyridazine (289 mg., 2 mmoles) and the mixture was heated at reflux for 17 hours. The excess *N,N*-dimethylformamide was removed *in vacuo* to afford a crude solid. This material was dissolved in a minimal amount of methanol, mixed with silica gel (*ca.* 2 g.), air-dried, and then evenly layered on the top of a silica gel column (2 x 12 cm., 12 g., slurry packed in chloroform). The column was eluted with chloroform (100 ml.) and then chloroform-methanol (98:2) with 20 ml. fractions being collected. Fractions 6-24 contained the faster moving component (major product) and fractions 26-50 contained the slower moving component. Fractions 6-24 were combined and evaporated under diminished pressure to furnish 240 mg. (72%) of 4-methylthioimidazo[4,5-*d*]-pyridazine (**5**). This heterocycle was found to be identical (mixture melting point, uv, ir, and ^{1}H nmr) to an authentic sample of **5** (6). Fractions 26-50 were pooled and evaporated to provide 24 mg. (8%) of imidazo[4,5-*d*]pyridazine-4-thione (**6**). This compound was shown to be identical (mixture melting point, uv, ir and ^{1}H nmr) to an authentic sample of **6** (6).

B. High Pressure Liquid Chromatographic (HPLC) Analysis.

Similar reaction conditions as described for A were employed. Prior to dissolving and injecting the crude solid for analysis, the inorganic residues were removed on a short, Kieselguhr pre-column (3.5 x 3.5 cm). The pre-column was eluted with chloroform-methanol (9:1) until all of the uv absorbing material was obtained. The eluent was then evaporated under diminished pressure to afford the solid mixture suitable for injection. The results of the HPLC analyses are summarized in Table I.

Reaction of 3-Methylthio-4,5-diaminopyridazine (**3**) with Sodium Methylmercaptide in *N,N*-Dimethylformamide.

A suspension of sodium methylmercaptide (500 mg., 7.1 mmoles) and **3** (300 mg., 1.92 mmoles) in dry *N,N*-dimethylformamide (10 ml.) was heated at reflux and the reaction was monitored by tlc (chloroform-methanol, 8:2). Within 3 hours, all of **3** was consumed and a new uv absorbing spot was detected. The reaction mixture was allowed to cool and then it was evaporated *in vacuo* to dryness. The crude material was applied to a short, Kieselguhr column (3.5 x 3.5 cm.) and eluted with chloroform-methanol (9:1). The resulting material (250 mg.) was subjected to hplc analysis (see Table I).

Reaction of 4,5-Diaminopyridazine-6-thione (**4**) with Sodium Methylmercaptide in *N,N*-Dimethylformamide.

To a suspension of sodium methylmercaptide (500 mg., 7.1 mmoles) in dry *N,N*-dimethylformamide (10 ml.) was added **4** (300 mg., 2.1 mmoles). The reaction mixture was heated at reflux for 17 hours and then worked up as described for **3**. The material (260 mg.) was analyzed by HPLC and the results are summarized in Table I.

Reaction of 4-Methylthioimidazo[4,5-*d*]pyridazine (**5**) with Sodium Methylmercaptide in *N,N*-Dimethylformamide.

4-Methylthioimidazo[4,5-*d*]pyridazine (**5**) (332 mg., 2 mmoles) was treated in the exact manner as **4**. The results are shown in Table I.

Demethylation of 3-Methylthio-4,5-diaminopyridazine (**3**) with Sodium Methylmercaptide in Methyl Sulfoxide.

A mixture of **3** (0.5 g., 3.2 mmoles) and sodium methylmercaptide (1.0 g., 14.2 mmoles) was heated in freshly distilled methyl sulfoxide (5 ml.) at 120°. Solution was effected in several hours and the heating was continued for 8 hours. At the end of this period, water (10 ml.) was added to the solution and the solution was stirred at room temperature for 10 hours while a gentle stream of air was bubbled through it. This process removed the final traces of methanethiol. The solution was then lyophilized and the residual solid was crystallized from 95% ethanol to furnish **4** (0.23 g., 50.5%). A mixture melting point, uv, and ir showed this heterocycle to be identical to an authentic sample of **4**.

Demethylation of 4-Methylthioimidazo[4,5-*d*]pyridazine (**5**) with Sodium Methylmercaptide in Methyl Sulfoxide.

4-Methylthioimidazo[4,5-*d*]pyridazine (**5**) (0.5 g., 3.0 mmoles) was treated in the exact manner as **3**. The residual solid obtained after lyophilization was dissolved in water and filtered through a Celite bed. The filtrate was acidified with concentrated hydrochloric acid to *p*H 1 and let stand overnight at room temperature. The crystalline material was removed by filtration and air-dried to provide **6** (0.15 g., 32.8%). This material was identical, in all respects, to an authentic sample of **6**.

Acknowledgments.

The authors wish to thank Professor Phyllis R. Brown and Dr. Richard A. Hartwick of the Department of Chemistry, University of Rhode Island for the use of their HPLC instrumentation and many helpful discussions concerning this project. We also thank Mrs. Anna Mary Albert and Ms. Sylvia Stoner for technical assistance.

REFERENCES AND NOTES

(1a) Presented in part at the 7th International Congress of Heterocyclic Chemistry, Tampa, Florida, August 1979, No. M1545C; (b) Recipient of a University of Rhode Island Graduate Fellowship 1979-80.

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(12) Two experiments were conducted to verify the formation of the postulated thiocarbonyl intermediate. The first involved heating only 4,5-diamino-3-methylthiopyridazine (**3**) in refluxing *N,N*-dimethylformamide. The second experiment involved an identical set of conditions with the exception that one equivalent of 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) (**3**:DBN = 1:1) was added. In both experiments, after 17 hours, the formation of 4-methylthioimidazo[4,5-*d*]pyridazine (**5**) was not observed. It is worth mentioning that in the presence of methylmercaptide ion **3** was converted to **5**, quantitatively, in 3 hours.

(13) The sensitivity of our hplc analysis is dependent on the extinction coefficients of the heterocycles shown in pathways A, B, and C. Although the ultraviolet spectra of 4-chloroimidazo[4,5-*d*]pyridazine are unknown we have used the data reported for 6-chloropurine (14). The ultraviolet spectra of these 4-substituted imidazo[4,5-*d*]pyridazines which we have synthesized and studied are quite similar, in all respects, to their purine counterparts. For example, imidazo[4,5-*d*]pyridazine-4-one; λ max (*p*H 1): 252.5 nm (5910); λ max (water): 256 nm (5640); λ max (*p*H 11): 259 nm (5800) is similar to hypoxanthine; λ max (*p*H 1): 248.5 nm (9940); λ max (water): 250 nm (10290); λ max (*p*H 11): 260 nm (10620). Based on the extinction coefficients for any of the heterocycles depicted, our calculations indicate that we should be able to detect them as low as 0.001%.

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(16) We are aware of only one other case of *S*-dealkylation of an aromatic heterocycle [see J. A. Montgomery, R. W. Balsiger, A. L. Fikes, and T. P. Johnson, *J. Org. Chem.*, **27**, 195 (1962)] which involved 7,8-dihydrothiazolo[2,3-*i*]purine with arylmercaptides in DMF. F. Bergmann and co-workers [Z. Neiman and F. Bergmann, *Israel J. Chem.*, **3**, 85 (1965); F. Bergmann, M. Rashi, U. Reichman, and Z. Neiman, *ibid.*, **8**, 919 (1970)] have reported on the *S*-demethylation of other *ortho*-quinoid type purines, however, in their work the methylthio group was displaced by a sulfide (or selenide) ion to generate the thioheterocycle rather than by S-CH_3 bond cleavage.

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(22) We wish to thank Ms. Betsy Baier and W. R. Grace & Co. for the gift of Raney Nickel No. 28 and No. 30.

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(24) Anhydrous sodium methylmercaptide was prepared and stored according to the published procedures of H. Plieninger (9b) and A. J. Fry (9a). Methanethiol was introduced either as a gas (Matheson) or as a liquid (Eastman). Solid sodium methylmercaptide which showed signs of discoloration was discarded and fresh material was prepared.