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1,4-Disubstituted Pyridazino[4,5-*d*]pyridazines

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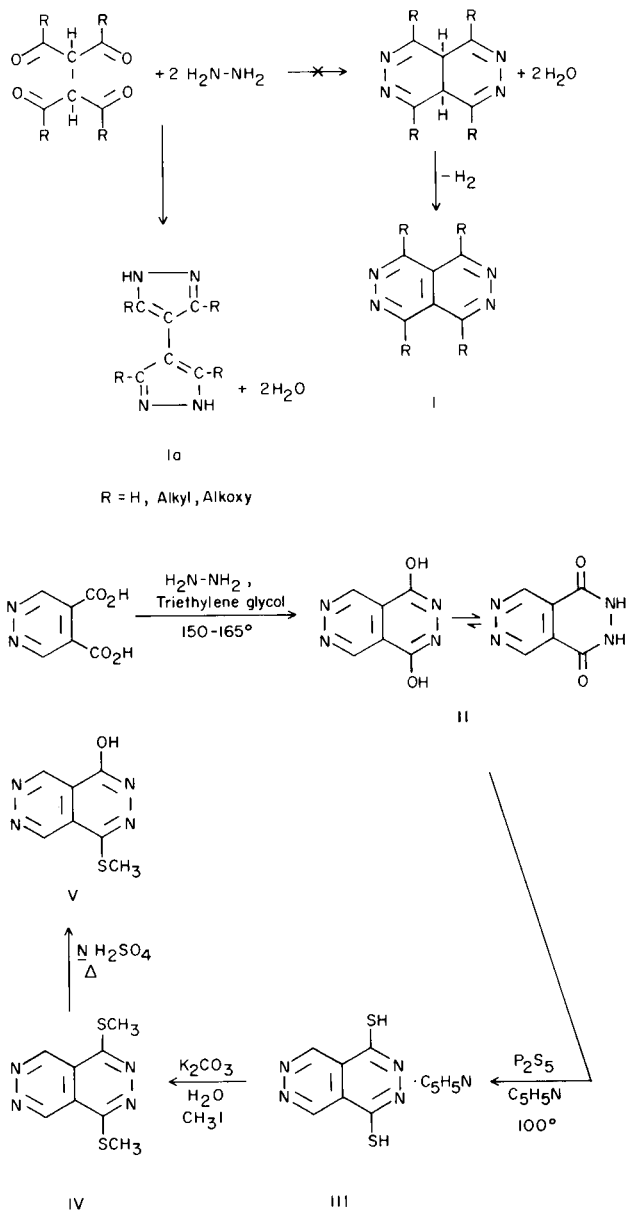
1,4-Bis(methylthio)pyridazino[4,5-*d*]pyridazine (IV) was synthesized from 4,5-pyridazinedicarboxylic acid in three steps. By employing IV as an intermediate, various 1,4-disubstituted pyridazino[4,5-*d*]pyridazine derivatives of classes 1,4-*N,S;* 1,4-*N,O;* 1,4-*O,S;* and 1,4-*O,O* were prepared by one-step or two-step nucleophilic substitution reactions. Steric, polar and resonance effects were observed in some of these reactions and are discussed.

In conjunction with some heterocyclic studies in this laboratory, we sought to prepare some pyridazino[4,5-*d*]-pyridazine derivatives. A search of the literature revealed that only a few pyridazino[4,5-*d*]pyridazine derivatives had ever been reported. These included 1,4,5,8-tetraphenylpyridazino[4,5-*d*]pyridazine (1), 5,8-dimethylpyridazino[4,5-*d*]pyridazine-1,4-diol (2), 1,4,5,8-bistrimethylenepyridazino[4,5-*d*]pyridazine (3) and 1,4,5,8-bis-β,β-dimethyltrimethylenepyridazino[4,5-*d*]pyridazine (3) (4). The pyridazino[4,5-*d*]pyridazine ring system appealed to us because it is related to simple pyridazines, phthalazines and pteridines, all of which display interesting chemical and biological properties (5).

At first inspection it appeared that the pyridazino-[4,5-*d*]pyridazine ring (I) system could be formed by condensation of two moles of hydrazine with a symmetrical tetracarbonyl ethane derivative. A dihydro pyridazino-[4,5-*d*]pyridazine would be produced from which, presumably, the fully unsaturated ring system could be obtained by aromatization. Such condensation reactions, however, proceed 1,3 instead of 1,4 to form the more stable, fully aromatic bi-pyrazole compounds (Ia) (2,6).

The next most practical route to the pyridazino[4,5-*d*]-pyridazine ring system was to start with one pyridazine ring intact and build on the second pyridazine ring. This was accomplished directly by condensing 4,5-pyridazinedicarboxylic acid with hydrazine in triethylene glycol using a modification of a procedure described by Fieser (7), pyridazino[4,5-*d*]pyridazine-1,4-diol (II) being obtained in 87% yield.

A number of unsuccessful attempts were made to replace the hydroxyl groups of II with chlorine using various phosphorus chloride reagents commonly used for this purpose in pyridazine (8), phthalazine (9) and pteridine (10) compounds. The hydroxyl groups of II, however, could be converted to thiol groups with phosphorus pentasulfide in pyridine (10). 1,4-Dithiopyridazino[4,5-*d*]-pyridazine (III) was isolated in the form of a 1:1 complex



with pyridine. Conversion of the dithiol (III) into 1,4-bis(methylthio)pyridazino[4,5-*d*]pyridazine (IV) was accomplished in aqueous potassium carbonate solution with methyl iodide. Reflux of IV in *N* sulfuric acid removed one of the methylthio groups forming V thus confirming the nmr data that the methyl groups were attached to sulfur and not nitrogen.

1,4-Bis(methylthio)pyridazino[4,5-*d*]pyridazine (IV) was subsequently employed as the intermediate for the preparation of other 1,4-disubstituted pyridazino[4,5-*d*]-pyridazines, mainly by stepwise nucleophilic substitution reactions.

1,4-*S*,*N* Derivatives.

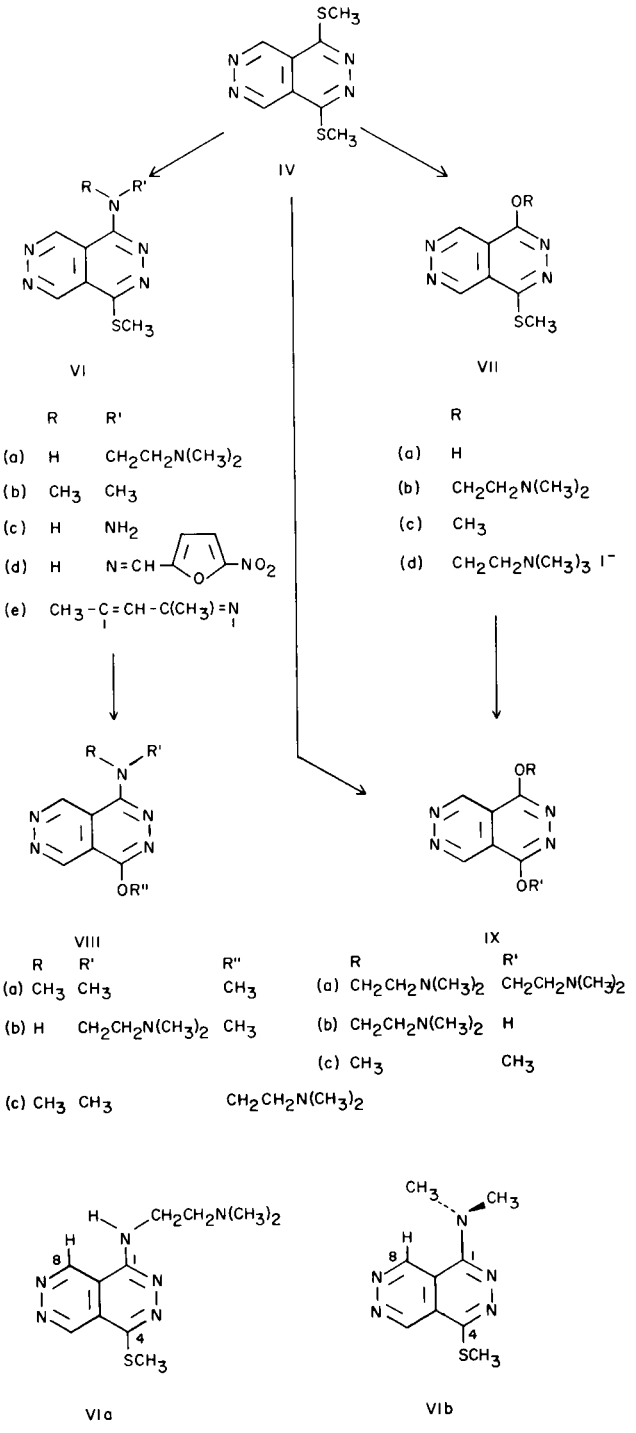
Generally, 1,4-*S*,*N* derivatives (VI) could be prepared by displacement of one of the methylthio groups of IV by primary or secondary amines. Reaction conditions appeared to differ substantially depending on the amine involved. Hydroxylic solvents, especially methanol, were avoided because nitrogen bases, excepting ammonia, were capable of inducing alkoxide formation. This point is discussed later. The nucleophilicity of the attacking base appeared to be a factor in the substitution reaction, *e.g.*, hydrazine reacted smoothly in acetonitrile solution at 70-80°, however ammonia was essentially unreactive even under more severe conditions. Steric effects also appeared to be involved in the substitution reaction of IV as indicated by its reactivity towards dimethylamine and piperidine. The dimethylamino derivative (VIb) was prepared from dimethylamine and IV in acetonitrile solution in moderate yield whereas no reaction between IV and piperidine occurred under comparable conditions. The last two 1,4-*S*,*N* derivatives (VId and VIe) were prepared by condensation of 1-hydrazino-4-(methylthio)pyridazino[4,5-*d*]-pyridazine (VIc) with 5-nitrofuraldehyde and acetylacetone, respectively. In none of the reactions of IV with amines was there observed any 1,4-diamino-substitution products.

1,4-*O*,*S* Derivatives.

1,4-*O*,*S* Derivatives (VII) were prepared directly (except VIId) from the bis(methylthio)pyridazino[4,5-*d*]pyridazine (IV) using an alkoxide or the corresponding alcohol and an amine catalyst. A 75% yield of the methoxy derivative (VIIc) was obtained from IV and methanol with piperidine as the catalyst.

The reaction of IV and 2-dimethylaminoethanol was sluggish. The 2-dimethylaminoethoxy derivative (VIIb) was obtained in about 31% yield (as the hydrobromide salt) from sodium 2-dimethylaminoethoxide and IV in 2-dimethylaminoethanol at room temperature. Formation of the monoether was accompanied by formation of the diether, 1,4-bis[2-(dimethylamino)ethoxy]pyridazino-[4,5-*d*]pyridazine (IXa), which was obtained in about 28% yield.

Treatment of the 2-dimethylaminoethoxy derivative (VIIb) with a mole of methyl iodide in acetone produced the corresponding choline derivative (VIId) in 95% yield. Methylation of the side chain tertiary amine group and not ring nitrogens or methylthio sulfur was confirmed by ultraviolet spectral data (an nmr spectrum was unobtainable because of the insolubility of the compound in available solvents). The spectrum of VIId (λ max (MeOH),



323 mμ, log ε 3.75) closely resembled that of the hydrobromide salt (λ max (MeOH), 323 mμ, log ε 3.78) of the starting material. Had ring or sulfur methylation occurred, most likely, the resulting perturbation of the ring system - the principle chromophore - would have been manifested by a substantially different UV spectrum.

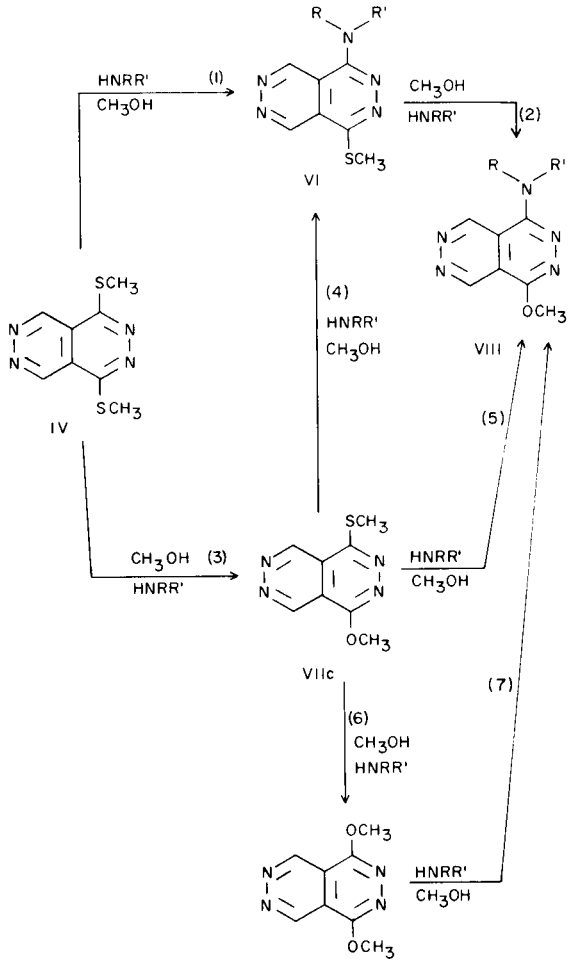
1,4-*O,N* Derivatives.

1,4-*O,N* Derivatives (VIII) were prepared from the corresponding methylthio compounds by displacement of the methylthio group by alkoxide (R″O-). The alcohol from which the alkoxide was derived was the solvent for the reaction. The ease with which the methylthio group was displaced was apparently influenced by the amine function of the starting compounds. When the 1-amine function was dimethylamine the 4-methylthio group could be displaced with sodium methoxide in a fairly dilute solution of methanol at 57° in 7-16.5 hours. Under comparable conditions, the methylthio group of 1-[(2-(dimethylamino)-ethyl)amino]-4-(methylthio)pyridazino[4,5-*d*]pyridazine was only slightly displaced by methoxide. Satisfactory results in this displacement reaction were achieved by using a more concentrated methanol solution, reflux temperature and a near equamolar amount of dimethylsulfoxide (DMSO). Of these conditions, DMSO appeared to contribute most in promoting this reaction, however, the reason is unclear. Its low concentration makes a significant solvent effect unlikely and the presence of much of it at the end of the reaction tends to negate any chemical participation in the reaction.

The greater ease by which the methylthio group can be displaced by the methoxyl group in the 1-(dimethylamino)-4-(methylthio) compound VIb as compared to the 1-[(2-dimethylamino)ethyl]amino-4-(methylthio) compound VIa can be rationalized on the basis of steric inhibition of resonance (14). Steric hindrance between the 8-hydrogen and the 1-dimethylamino group would tend to force the latter out of coplanarity with the ring thereby reducing the mesomeric release of electrons into the ring. Such an effect would lower the electron density at C_4 and make the methylthio group more susceptible to nucleophilic displacement (11). On the other hand, the lower steric requirement of the 1-[(2-dimethylamino)ethyl]amino group in VIa would allow for a more favorable coplanar arrangement of the amino function with the ring thereby increasing the relative mesomeric release of electrons into the ring and the electron density at C_4. Thus, the susceptibility of the methylthio group to nucleophilic displacement in VIa would be less compared to that in VIb.

As mentioned previously reaction attempts to prepare 1,4-*S,N* derivatives (VI) from 1,4-bis(methylthio)pyridazino[4,5-*d*]pyridazine (IV) and amines in methanol gave various alkoxide derivatives (VIIc, VIII, IX) as the main products or side reaction products depending on the amine and reaction conditions. The interrelation and possible pathways between products of these reactions are outlined in Scheme I. Only in the reactions of dimethylamine was an 1,4-*O,N* product (VIII) formed. When IV was heated at 55° with dimethylamine in methanol for 43 hours, there was obtained a mixture of VI (R,R′ = methyl) and VIII (R,R′ = methyl) in composite yields of 51 and 8%, respectively. Since no 1-(methylthio)-4-methoxypyridazino[4,5-*d*]pyridazine (VIIc) or 1,4-dimethoxy derivative (IXc) was observed route (1-2) was implicated as the probable pathway to the 1,4-*O,N* derivative (VIII). This was supported by increasing the reaction time which resulted in a smaller ratio of VI to VIII. The feasibility of route (1-2) was demonstrated by heating VI (R,R = methyl) with piperidine in methanol at 55° for three days. A 50:50 mixture of VI and VIII (R,R′ = methyl) were the only perceptible products (via nmr). Finally, routes (3-5 and 3-6-7) were shown to be unlikely for the formation of

SCHEME I



VIII (R,R′ = methyl) by the following experiment. Heating a 9:1 molar mixture of the 1-(methylthio)-4-methoxypyridazino[4,5-*d*]pyridazine (VIIc) and 1,4-dimethoxypyridazino[4,5-*d*]pyridazine (IXc) respectively, in methanolic dimethylamine produced a mixture (R,R′ = methyl) containing 56% (molar) 1,4-*N,S* derivative (VI), 6% 1,4-*O,N* derivative (VIII), 17% VIIc and 21% IXc.

Clearly, the principal mode of reaction of VIIc with dimethylamine is the preferential displacement of methoxyl compared to methylthio to form VI; the small amount of VIII formed may have actually resulted from methanolysis of VI as well as directly from VIIc. The relative build-up of the dimethoxy derivative (IXc) during the reaction as well as the low formation of VIII, indicates that the displacement of methoxyl from 1,4-dimethoxypyridazino[4,5-*d*]pyridazine (IXc) by dimethylamine is slower than displacement of methoxyl from 1-methoxy-4-(methylthio)pyridazino[4,5-*d*]pyridazine (VIIc).

The preferential displacement of methoxyl as compared to methylthio in 1-methoxy-4-(methylthio)pyridazino[4,5-*d*]pyridazine (VIIc) by amines appears to be general as similar results were obtained in reactions with hydrazine and *N,N*-dimethylethylenediamine (see Experimental Section). These results appear to be in line with the findings of Hill and Krause (11) in their rate study of nucleophilic aromatic substitution of chloride by methoxide from a series of 3-chloropyridazines variously substituted in the 6-position. First, electron-withdrawing substituents in the 6-position facilitated displacement of chloride. The ρ value (from plot of log k vs. σ) for this substitution reaction is very high, +6.82, indicating that the reaction is quite sensitive to the nature of the 6-substituent as reflected by changes in the electron density at the 3 carbon atom. Thus, the greater tendency for displacement of the methoxyl group compared to the methylthio group in VIIc by the dimethylamino group can be attributed in part to the fact that the methylthio group (σ = -0.047) (12) exerts a stronger substituent effect on the nucleophilic displacement of the methoxyl group (σ = -0.268) (12) than does the methoxyl group on the methylthio group.

1,4-*O,O* Derivatives.

1,4-*O,O* Derivatives (IX) were obtained, for the most part, inadvertently from alkoxide reactions with 1,4-bis-(methylthio)pyridazino[4,5-*d*]pyridazine (IV) and 1-methoxy-4-(methylthio)pyridazino[4,5-*d*]pyridazine (VIIc) or to slight extent from IV and some amines in methanol as in the case of IXc. The reaction of VIIc and sodium 2-(dimethylamino)ethoxide gave symmetrical 1,4-dialkoxy derivative IXa and a small amount of IXb. Formation of IXa is not surprising since alkoxy exchange in pyridazines has been well demonstrated (13). Formation of IXb was unexpected and is believed to have occurred either during the reaction or inadvertently in the reaction workup.

EXPERIMENTAL

Melting and boiling points are uncorrected. Melting points were recorded in open capillaries. Infrared spectra were recorded as specified on a Perkin-Elmer grating spectrophotometer, model 337. Ultraviolet spectra were obtained with a Perkin-Elmer spectrophotometer, model 202. Nmr spectra were recorded on a Varian A-60 spectrometer.

4,5-Pyridazinedicarboxylic Acid.

4,5-Pyridazinedicarboxylic acid was obtained by permanganate oxidation of phthalazine using a procedure similar to that described by Jones and McLaughlin (15) to prepare 2,3-pyrazinedicarboxylic acid.

Pyridazino[4,5-*d*]pyridazine-1,4-diol (II).

Modification of a procedure described by Fieser (7) for the preparation of 5-nitro-1,4-phthalazdione was followed. A stirred mixture of 216 g. (1.29 moles) of 4,5-pyridazinedicarboxylic acid, 450 ml. of water and 70 g. (1.40 moles) of 64% hydrazine were heated to about 95° to effect solution; 500 ml. of triethylene glycol was added and the resulting solution was further heated (flame or mantle) and stirred to expel water. To facilitate removal of water a glass tube connected to a vacuum source was suspended about four or more inches above the solution's surface.

The reaction temperature rose slowly and at *ca.* 150° (~50 minutes required) precipitation of a yellow solid began. Heating in the range 150-165° was continued for 2.5 hours. When the temperature had dropped to 100° the reaction mixture was diluted with 2 l. of hot water. After standing overnight at room temperature the product was removed by filtration, washed with water and dried to afford 146 g. of tan powder. Addition of *ca.* 25 ml. of acetic acid to the mother liquor gave, after standing 2 days, a second crop of 37.4 g. making the total yield 183.4 g. (87%), m.p. >315°. The product was purified for analysis by dissolving a sample in dilute ammonia, filtering and reprecipitating the diol with 5*N* hydrochloric acid as a light tan powder; infrared (Nujol): ν, 3185, 2450 (very broad), 1770 (weak, broad), 1685 (sharp), 1585 (sharp) cm^{-1}.

Anal. Calcd. for $C_6H_4N_4O_2$: C, 43.9; H, 2.46; N, 34.14. Found: C, 44.1; H, 2.54; N, 34.20.

1,4-Dithiopyridazino[4,5-*d*]pyridazine (III).

To a stirred suspension of 168 g. (1.025 moles) of 1,4-pyridazino[4,5-*d*]pyridazinediol in 3 l. of redistilled pyridine under a constant atmosphere of carbon dioxide was added cautiously in tablespoon portions, 500 g. (2.25 moles) of phosphorus pentasulfide (m.p. 278-280°). About 20 minutes were required for the addition during which time the reaction temperature did not exceed 60°. The reaction mixture was then heated at 98-101° for 2 hours, solution resulting. The bulk (1.8-2 l.) of pyridine was removed from the reaction mixture by distillation at *ca.* 35-40 mm. and a pot temperature of 40-50° with continued stirring. When the concentration was complete the reaction residue, a thick, black, mobile paste, was chilled to about 10-13° and atmospheric pressure was restored with nitrogen. Under a nitrogen atmosphere was then added, very cautiously, with continued cooling and stirring cold 2 *N* ammonia, initially several drops at a time. The ensuing reaction, release of hydrogen sulfide and frothing, was allowed to subside before adding more ammonia. The quantity of ammonia that could be added safely, *i.e.*, holding the reaction temperature

below 30° and limiting excessive frothing, gradually increased until further additions caused no change in the mixture. A total of 8 l. of cold 2 *N* ammonia was added, the last half rapidly. This mixture was allowed to warm to room temperature and stirred for 5 hours, the nitrogen atmosphere being maintained. After dividing into two portions, the ammoniacal solution was quickly acidified to *p*H 5 with a total of 500 ml. of glacial acetic acid. The resulting mixtures were refrigerated for several days and the product was collected on one filter, washed well with water and dried yielding 181.7 g. of maroon prisms, m.p. 203-206° dec. with gas (alkaline to wet litmus) evolution. The product crystallizes with pyridine; heating a sample at 200° in a mass spectrometer produces an intense spectrum of pyridine. The crude dithiol was dissolved in dilute ammonia and filtered through filter-aid free of apparent inorganic impurities. The filtrate was diluted with a little pyridine, acidified to *p*H 4-5 with acetic acid and seeded. There was obtained dark bronze crystals, m.p. 206-209° dec. with prior discoloration beginning around 199°. Recrystallization from dimethylformamide (maximum solution temperature 80°) afforded the analytical 1:1 pyridine complex of the dithiol (16) as a reddish-brown solid which decomposed without melting above 180°

Anal. Calcd. for $C_6H_4N_4S_2 \cdot C_5H_5N$: C, 48.0; H, 3.29; N, 25.4; S, 23.3. Found: C, 47.6; H, 3.54; N, 25.7; S, 23.2.

1,4-Bis(methylthio)pyridazino[4,5-*d*]pyridazine (IV).

Seven hundred milliliters of water were stirred and evacuated to *ca.* 10 mm. to remove dissolved oxygen, atmospheric pressure being restored with nitrogen. This step was repeated whereupon 39.2 g. (0.2 mole assuming 1:1 dithiol:pyridine complex) of 1,4-dithiopyridazino[4,5-*d*]pyridazine and 70 g. (0.5 mole) of potassium carbonate were added to the water and the stoppered mixture was shaken vigorously, then stirred for 10 minutes. Insoluble impurities were allowed to settle and the solution was filtered by suction, care being taken to avoid pulling excess air through the filter. After washing the filter residue with water, the filtrate was transferred in equal volumes to three Parr shaker bottles that had been flushed with nitrogen. To each bottle was added 7.7 ml. (total, 0.4 mole) of methyl iodide; these were rubber stoppered and shaken (a Parr shaker was used) for 1.5 hours. The crude bis(thioether) (IV) was collected, washed well, and dried yielding a total of 28.7 g. of a dark brown powder. Recrystallization from *ca.* 650 ml. of 1,2-dimethoxyethane afforded 18.8 g. (38% from the diol) of dark brown stout needles and rods (the product from ethanol has a light golden yellow appearance), m.p. 192-193.5°. Ultraviolet: λ max (MeOH), 232 (log ε 3.94) and 348 (log ε 3.92) mμ. Nmr (deuteriochloroform): -2.85 (singlet, $-SCH_3$) and -9.75 (singlet, ring protons) ppm (TMS).

Anal. Calcd. for $C_8H_8N_4S_2$: C, 42.8; H, 3.60; N, 24.98; S, 28.59. Found: C, 43.0; H, 3.63; N, 24.75; S, 28.74.

1-Hydroxy-4-(methylthio)pyridazino[4,5-*d*]pyridazine (VIIa).

A sample of 124 mg. of the bis(thioether) IV was refluxed in 20 ml. of *N* sulfuric acid for one hour, complete solution resulting with concomitant release of methanethiol. On standing needle-like crystals separated from the solution and these were collected, washed and dried yielding 76 mg. (71%) of 1-hydroxy-4-(methylthio)pyridazino[4,5-*d*]pyridazine VIIa, m.p. 249-250°; Infrared (Nujol); ν, 3215 and 3150 (weak, NH/OH), 1680 (strong, C=O) and 680 (SCH_3) cm^{-1}.

Anal. Calcd. for $C_7H_6N_4OS$: C, 43.3; H, 3.11; N, 28.85; S, 16.51. Found: C, 43.6; H, 3.16; N, 29.03; S, 16.59.

1-(Dimethylamino)-4-(methylthio)pyridazino[4,5-*d*]pyridazine (VIb).

A mixture 6.0 g. (0.0267 mole) of 1,4-bis(methylthio)-pyridazino[4,5-*d*]pyridazine (m.p. 187-189°) and 300 ml. of dimethylamine in acetonitrile (3.1 *N*) was rocked in a 500 ml. stainless steel bomb at 65-70° for 24 hours. When cooled to room temperature the reaction solution was treated with 3 g. of Darco, filtered and freed of volatile materials and solvent *in vacuo*. The residue was taken up in 140 ml. of ethanol, treated with 1 g. of Darco and filtered. Crystallization of the product was allowed to proceed at 30-35° after seeding. There was obtained 2.5 g. (42%) of soft, yellow solid, m.p. 161-162°. A second recrystallization from ethanol afforded the analytical sample, the melting point was unchanged. Ultraviolet: λ max (MeOH), 210 (log ε 4.09), sh 245 (log ε 4.01) and 363 (log ε 3.83) mμ; nmr (deuteriochloroform): -2.81 (singlet, $-SCH_3$), -3.34 (singlet, $-N(CH_3)_2$), -9.78 and -9.85 (doublets J ≅ 1.8 cps, ring protons) ppm (TMS).

Anal. Calcd. for $C_9H_{11}N_5S$: C, 48.9; H, 5.01; N, 31.7; S, 14.5. Found: C, 48.9; H, 4.82; N, 31.9; S, 14.7.

A higher yield (48%) of this product (m.p. 158-159°) was obtained from a similar run in which the crude reaction mixture was chromatographed on a silica gel (200-325 mesh) column (*ca.* 0.95 x 8.5″). The reaction mixture was introduced to the column as a concentrated benzene solution. The column was then developed with carbon tetrachloride (100 ml.) and methylene chloride (100 ml.), the product eluted with methylene chloride: methanol (50:1 to 50:10, *ca.* 250 ml. total) and recrystallized from ethanol.

1-[(2-Dimethylamino)ethyl]amino-4-(methylthio)pyridazino[4,5-*d*]pyridazine (VIa).

A stirred mixture of 7 g. (0.0312 mole) of 1,4-bis(methylthio)-pyridazino[4,5-*d*]pyridazine and 50 ml. of *N,N*-dimethylethylenediamine, protected from atmospheric moisture and carbon dioxide with Drierite and Ascarite, was heated at 90-95° for 50 minutes, the evolution of methanethiol was observed by ebulition in the resulting solution. Unchanged *N,N*-dimethylethylenediamine was removed *in vacuo* and the residue was triturated in 100 ml. of *N* hydrochloric acid (additional 5 *N* hydrochloric acid was added, if necessary, to lower *p*H to *ca.* 1) and the resulting mixture was transferred to a separatory flask and extracted twice with 60 ml. portions of methylene chloride. The aqueous layer was then decolorized with Darco, filtered and the filtrate basified with concentrated ammonia to *p*H >9. This mixture was extracted with five 50-ml. portions of methylene chloride. The combined, dried (magnesium sulfate) extracts were concentrated to about 15-20 ml. and diluted slowly, while gently warming, with a total of 175 ml. of ether. The golden yellow needles that formed were collected after crystallization was complete; obtained 6.2 g. (75%), m.p. 140-141.5°; Ultraviolet: λ max (MeOH), 359 (log ε 3.79) mμ; nmr (deuteriochloroform): -2.32 (singlet, $-N(CH_3)_2$), -2.70 and -2.78 (triplet, $-CH_2-NMe_2$ and singlet, $-SCH_3$), -3.77 (triplet, $-NH-CH_2-$), -9.68 and -9.84 (ring protons) ppm (TMS).

Anal. Calcd. for $C_{11}H_{16}N_6S$: C, 50.0; H, 6.10; N, 31.79; S, 12.13. Found: C, 50.3; H, 6.33; N, 31.90; S, 12.11.

Reaction of 1,4-Bis(methylthio)pyridazino[4,5-*d*]pyridazine and Dimethylamine in Methanol.

A mixture of 3 g. (0.0134 mole) of 1,4-bis(methylthio)-pyridazino[4,5-*d*]pyridazine and 140 ml. of 5 *N* methanolic dimethylamine was heated at 55° in a stoppered pressure bottle for 43 hours, the mixture being shaken at times. After removal of amine and methanol the residue was recrystallized from ethanol to afford 1.3 g. of yellow fluffy crystals, m.p. 154.5-156°. This material consisted (by nmr analysis) of 1-dimethylamino-4-(methylthio)pyridazino[4,5-*d*]pyridazine (VIb) and 1-dimethylamino-4-

methoxypyridazino[4,5-*d*]pyridazine (VIIIa), 90 and 10 mole percent, respectively. The mother liquor was evaporated to dryness and the residue (1.6%) was recrystallized from *ca.* 15 ml. of ethanol affording a second crop of 0.42 g., m.p. 138-144°. Nmr analysis showed this crop to contain the above named products in respective mole percents of 73 and 27 making the overall respective yields of 51 and 8.2%.

The second crop was subjected to further heating in methanolic dimethylamine for 5 days. The nmr spectrum of the residue recovered after evaporation of amine and methanol showed the relative proportions of VIb and VIIIa to be 43 and 57 mole percent, respectively. Absorptions of minor impurities were also observed.

1-Hydrazino-4-(methylthio)pyridazino[4,5-*d*]pyridazine (VIc).

A saturated solution of 22.4 g. (0.10 mole) of ground 1,4-bis-(methylthio)pyridazino[4,5-*d*]pyridazine in 400 ml. of acetonitrile was treated with 15 ml. (*ca.* 0.44 mole) of anhydrous hydrazine (95%) and this mixture was heated (hood) at 75-81° for *ca.* 1.25 hours with intermittent stirring. Methanethiol was evolved from the beginning of the reaction and the product began separating before solution of the starting material was complete. When cooled, the reaction mixture was refrigerated overnight and filtered. The filter cake was washed well and when dried appeared as a dark brown solid, 15.4 g.; concentration of the mother liquor to *ca.* 80 ml. and further heating of the residue produced a second crop of 4.2 g. The crops were combined, triturated in 800 ml. of *N* hydrochloric acid and filtered, insolubles, *i.e.* starting material and and by-products, were collected on the filter. After washing of the filter residue (triturated filter residue in 300 ml. of hot 1,2-dimethoxyethane and filtered with suction while hot; the filtrate was concentrated to *ca.* 200 ml., Darco treated while hot, and filtered. There was obtained 5.0 g. of the starting bismethylthio ether from the chilled filtrate, m.p. 193-195°) with *N* hydrochloric acid and water the filtrate was treated with Darco, filtered, and the filtrate basified with ammonia (7-8 *N*) precipitating the hydrazino product. This was collected on a filter after the mixture had been chilled for *ca.* 3 hours, washed well with water and dried *in vacuo* at 45°. There was obtained a light brown solid, 10.3 g. (64%), which was unstable on standing at room temperature and decomposed without melting above about 168°; infrared (Nujol mull): ν, 3375, 3260 and 3200 ($NH\text{-}NH_2$) cm^{-1}; nmr (trifluoroacetic acid): -2.82 (singlet, $-SCH_3$) and -10.2 and -10.6 (singlets, ring protons) ppm (TMS). The hydrobromide salt could be precipitated from 48% hydrobromic acid and 2-propanol as light brown flakes, m.p. 208-210° dec., depending on rate of heating. Crystallization of this material from methanol gave the hydrobromide monomethylate, m.p. 201°, decomposing sharply with gas evolution. Further recrystallization from water-2-propanol produced the hydrobromide monohydrate, m.p. 201-202° dec., light brown, buff crystalline solid.

Anal. Calcd. for $C_7H_9BrN_6S\cdot H_2O$: C, 27.4; H, 3.61; N, 27.36; Br, 26.02; S, 10.44. Found: C, 28.0; H, 3.52; N, 27.54; Br, 25.90; S, 10.43.

5-Nitro-2-furaldehyde (4-(Methylthio)pyridazino[4,5-*d*]pyridazin-1-yl)hydrazone (VId).

To a slurry of 8.0 g. (0.0385 mole) of 1-hydrazino-4-(methylthio)pyridazino[4,5-*d*]pyridazine (VIc) in 80 ml. of ethanol was added 6.0 g. (0.042 mole) of 5-nitro-2-furaldehyde. This mixture was stirred vigorously as the red product formed. After stirring intermittently for one hour, a second 6 g. portion of the aldehyde was added and the mixture heated at 70° with stirring until it appeared that all of the hydrazino starting material (tan colored) had reacted. After standing several days, the product was collected on a filter, washed and dried yielding 11.5 g. (91%) of red solid, m.p. 238.5-240° dec. The crude product was recrystallized from 1750 ml. of DMF (maximum temperature, 95°) to afford 8.1 g. of fine maroon crystals. Nmr (trifluoroacetic acid) showed the presence of residual DMF and this was removed by twice stirring in 200 ml. of warm water for about 4 hours, the appearance of the crystals remaining the same, 7.6 g., m.p. 246-246.5° dec.; nmr (trifluoroacetic acid): -2.88 (singlet, $-SCH_3$), -7.36 and -7.57 (pair of AB doublets ($J \cong 4.5$ cps), furan ring protons), -8.71 (singlet, -N=C-H) and -10.2 and -10.8 (singlets, pyridazine ring protons) ppm (TMS).

Anal. Calcd. for $C_{12}H_9N_7O_3S$: C, 43.5; H, 2.74; N, 29.60; S, 9.68. Found: C, 43.4; H, 2.87; N, 29.35; S, 9.61.

1-(3,5-Dimethylpyrazol-1-yl)-4-(methylthio)pyridazino[4,5-*d*]-pyridazine (VIe).

A mixture of 4.0 g. (0.0192 mole) of 1-hydrazino-4-(methylthio)-pyridazino[4,5-*d*]pyridazine (VIc) and 20 ml. of acetylacetone was stirred, the hydrazino material dissolved as the product precipitated. This mildly exothermic reaction was allowed to stand for 1.75 hours then 80 ml. of ethanol was added and this mixture was triturated at *ca.* 70°, allowed to cool and the product was removed by filtration, washed and dried. There was obtained 4.65 g. (89%) of light tan solid, m.p. 225-226°. Recrystallization from 800 ml. of absolute ethanol afforded 4.25 g. (82%) of light yellow fibers, m.p. 226-227°; ultraviolet: λ max (MeOH), 233 (log ϵ 4.06) and 339 (log ϵ 4.06) mμ; nmr (trifluoroacetic acid): -2.59 and -2.70 (singlets, $-CH_3$), -3.12 (singlet, $-SCH_3$), -6.82 (singlet, pyrazole ring proton) and -10.10 and -10.35 (singlets, pyridazine ring protons) ppm (TMS).

Anal. Calcd. for $C_{12}H_{12}N_6S$: C, 52.9; H, 4.44; N, 30.86; S, 11.77. Found: C, 53.1; H, 4.67; N, 30.87; S, 11.88.

1-[2-(Dimethylamino)ethoxy]-4-(methylthio)pyridazino[4,5-*d*]-pyridazine Hydrobromide (VIIb).

Redistilled 2-dimethylaminoethanol, 160 ml., and 1.14 g. of sodium hydride mineral oil dispersion (52.5% sodium hydride) were stirred with the exclusion of atmospheric moisture and carbon dioxide. When the evolution of hydrogen had subsided, 12 g. (0.0536 mole) of 1,4-bis(methylthio)pyridazino[4,5-*d*]pyridazine and the resulting mixture was stirred at room temperature for 3.25 hours whereupon a solution, prepared from 0.928 g. of sodium hydride mineral dispersion (total moles of sodium hydride 0.0457) and 40 ml. of 2-dimethylaminoethanol, was added and stirring was continued for 1.75 hours. The reaction was quenched by the addition of 4 ml. (0.067 mole) of acetic acid. The reaction mixture was freed of 2-dimethylaminoethanol *in vacuo* (vacuum pump) with the aid of a rotary evaporator. The residue was diluted with 100 ml. of hydrochloric acid and sufficient 6 *N* hydrochloric acid was added to lower the *p*H of the solution of *ca.* 5-6; this was extracted twice with 50 ml. portions of methylene chloride (to remove mineral oil and unchanged starting material). The aqueous layer was filtered through filter-aid to break up some resulting emulsion, then treated with Darco and filtered. The filtrate was basified with concentrated ammonia (to *ca.* *p*H >9.8) and extracted five times with methylene chloride. The combined and dried (magnesium sulfate) extracts were evaporated and the residue, a dark thick oil of 12.9 g., was chromatographed on a silica gel (200-325 mesh) column (1.2 x 12"). The mixture was introduced to the column as a concentrated benzene solution. The column was first eluted with methylene chloride (150 ml.) and 2.0 g. (28%, based on hydride used) of crude 1,4-bis(2-(dimethylamino)ethoxy)pyridazino[4,5-*d*]pyridazine (IXa) was obtained in this fraction. The column was further eluted with methylene chloride-methanol (50:2, 104 ml.), (50:5, 330 ml.) and (50:10, 360 ml.). The

product, 7.6 g., was obtained in the last fractions and recrystallized in two parts, 5.40 and 2.29 g. from 80 and 40 ml. of cyclohexane, respectively; there was obtained 2.75 (m.p. 55-70°) and 1.2 (m.p. 67-77°) g., respectively. Treatment of the former with 54 ml. of 0.24 *N* hydrobromic acid in isopropyl alcohol precipitated 3.45 g. (31% based on hydride used) of the hydrobromide salt, white solid, m.p. 214-215° dec., and 218-218.5° dec., after recrystallization from dilute alcohol. Ultraviolet: λ max (MeOH), 323 (log ε 3.78) mμ; nmr (deuterium oxide): -2.74 (singlet; SCH_3), -3.21 (singlet, $N(CH_3)_2$), -4.01 (triplet, $-CH_2-N$) and -5.11 (triplet, $-CH_2-O-$) -9.68 and -10.0 (doublets J ≅ 2 cps, ring protons) ppm (TMS Na salt).

Anal. Calcd. for $C_{11}H_{16}BrN_5OS$: C, 38.2; H, 4.66; N, 20.23; S, 9.26; Br, 23.1. Found: C, 38.5; H, 4.58; N, 20.23; S, 9.11; Br, 23.0.

1,4-Bis(2-(dimethylamino)ethoxy)pyridazine Dihydrobromide (IXa).

Crude 1,4-bis(2-(dimethylamino)ethoxy)pyridazino[4,5-*d*]-pyridazine (see previous experiment) was further purified by chromatography on a silica gel column (0.95 x 10.5") as before, eluting the desired product with carbon tetrachloride. Treatment of 0.6 g. of this material with hydrogen bromide in isopropyl alcohol precipitated the dihydrobromide salt, 0.75 g., which after recrystallization from dilute alcohol (Darco) yielded 0.34 g. of soft, beige needles, m.p. 248.5-250° dec.; nmr (deuterium oxide): -3.18 (singlet, $-N(CH_3)_2$), -.392 (triplet, $-CH_2N$), -5.10 (triplet, $-CH_2O-$) and -10.10 (singlet, ring protons) ppm (TMS Na salt).

Anal. Calcd. for $C_{14}H_{24}Br_2N_6O$: C, 35.9; H, 5.17; N, 17.95. Found: C, 35.9; H, 5.38; N, 17.74.

(2-[(4-(Methylthio)pyridazino[4,5-*d*]pyridazin-1-yl)oxy]ethyl)-trimethylammonium Iodide (VIId).

A solution of 1.2 g. (0.0045 mole) of 1-[2-(dimethylamino)-ethoxy]-4-(methylthio)pyridazino[4,5-*d*]pyridazine (m.p. 67-77°, see above) in 25 ml. of acetone was treated with 0.76 g. (0.0053 mole) of methyl iodide. Shortly after, the product precipitated as small tan-yellow crystals which after isolation, washing and drying amounted to 1.73 g. (95%), m.p. 233.5-234°, sharp with dec. Recrystallization from methanol afforded yellow plates of the hemi-methylate, m.p. 236-236.5°. Infrared (Nujol mull): ν, 3410 (OH) cm^{-1}; ultraviolet: λ max (MeOH), 215 (log ε 4.33) and 323 (log ε 3.75) mμ. Methanol in VIId was confirmed by a mass spectral analysis.

Anal. Calcd. for $C_{12}H_{18}IN_5OS \cdot \frac{1}{2}CH_3OH$: C, 35.5; H, 4.76; N, 16.55; I, 30.0; S, 7.58. Found: C, 35.3; H, 4.36; N, 16.68; I, 29.7; S, 7.50.

1-Methoxy-4-(methylthio)pyridazino[4,5-*d*]pyridazine (VIIc).

A stoppered mixture of 5.0 g. (0.0223 mole) of 1,4-bis-(methylthio)pyridazino[4,5-*d*]pyridazine, 10 ml. of dry piperidine and 350 ml. of warm methanol (45°) in a Parr pressure bottle was heated at *ca.* 57° for 24 hours, bottle pressure being released occasionally. The reaction solution was evaporated *in vacuo* to dryness and the residue was recrystallized from 40 ml. of methanol to afford 3.5 g. (75%) of short, Khaki-colored needles, m.p. 153-154.5°. The composition of this material was determined by nmr analysis to be *ca.* 96% product and 4% 1,4-dimethoxypyridazino[4,5-*d*]pyridazine (IXc) based on the integration of the methylthio and methoxyl absorptions of the former, -2.83 and -4.33 ppm (TMS), respectively, and on the methoxyl absorption of the latter, -4.29 ppm (ring protons for VIIc absorb at *ca.* -9.73 and -9.86 ppm masking the ring proton absorption of IXc). The analytical sample was obtained by three additional recrystallizations from methanol, m.p. 156-157°.

Anal. Calcd. for $C_8H_8N_4OS$: C, 46.1; H, 3.88; N, 26.91; S, 15.4. Found: C, 46.2; H, 3.72; N, 27.10; S, 15.3.

1-(Dimethylamino)-4-methoxypridazino[4,5-*d*]pyridazine (VIIIa).

T To a saturated solution of 7.2 g. (0.0325 mole) of 1-(dimethylamino)-4-(methylthio)pyridazino[4,5-*d*]pyridazine (VIb) and 350 ml. of methanol in a Parr shaker bottle was added at 40-45° 1.75 g. (0.0325 mole) of sodium methoxide in 3 portions. The reaction bottle was closed with a rubber stopper, shaken, and heated at 57° for 7 hours, pressure build-up within the bottle being relieved by intermittent opening. Complete solution resulted within 2 hours of heating. After heating, 1.9 ml. (0.0325 mole) of acetic acid was added and solvent was removed from the reaction mixture *in vacuo*. The solid yellow residue was dissolved in a solution of chloroform (100 ml.) and methylene chloride (125 ml.), washed twice with water and once with saturated salt solution, dried (magnesium sulfate) and evaporated *in vacuo*. A nmr analysis of the residue (6.85 g.) showed the crude material to consist of *ca.* 94% product (corresponding to *ca.* a 96% yield) and 6% starting material. After recrystallization from 80 ml. of isopropyl alcohol there was obtained 4.2 g. of bright yellow fibers, m.p. 123.5-124.5°. The composition of this material was about the same as the crude product.

In another run, 2.2 g. of material (94% product and 4% starting material) and 0.8 g. of material (9% product and 91% starting material) were combined (equiv. to 0.004 mole of starting material) and treated as previously with 0.267 g. (0.005 mole) of sodium methoxide in 250 ml. of methanol at 57°, the reaction period being extended to 16.5 hours. The reaction mixture was worked up as before and the crude product was recrystallized from 35 ml. of isopropyl alcohol. There was obtained 1.9 g. of soft yellow fiber, m.p. 125-126.5°. The nmr (deuteriochloroform) spectrum of this material was virtually free of starting material showing absorptions at -3.25 (singlet, $-N(CH_3)_2$), -4.26 (singlet, $-OCH_3$) and -9.78 (singlet, 2 ring protons) ppm (RMS); ultraviolet: λ max (MeOH), 342 (log ε 3.71) mμ.

Anal. Calcd. for $C_9H_{11}N_5O$: C, 52.7; H, 5.40; N, 34.13. Found: C, 52.8; H, 5.43; N, 34.30.

Piperidine Catalyzed Methanolysis of 1-Dimethylamino-4-(methylthio)pyridazino[4,5-*d*]pyridazine (VIb).

A solution of 0.208 g. of 1-dimethylamino-4-(methylthio)-pyridazino[4,5-*d*]pyridazine, 0.2 g. of piperidine in 10 ml. of methanol was heated at 55° for 3 days. The amine and methanol was removed *in vacuo* and the nmr of the residue showed it to be a 50:50 mixture of starting material and 1-dimethylamino-4-methoxy-pyridazino[4,5-*d*]pyridazine (VIIIa).

1-[(2-(Dimethylamino)ethyl)amino]-4-methoxypyridazino[4,5-*d*]-pyridazine (VIIIb).

(A) A solution of 4.0 g. (0.015 mole) of 1-[(2-(dimethylamino)-ethyl)amino]-4-(methylthio)pyridazino[4,5-*d*]pyridazine (VIa) and 0.82 g. (0.015 mole) of sodium methoxide in 200 ml. of methanol was heated in a stoppered Parr shaker bottle at 57° for 12 hours. After addition of 0.95 ml. (0.016 mole) of acetic acid the reaction mixture was freed of solvent *in vacuo* and the residue was partitioned between 125 ml. of methylene chloride and dilute bicarbonate solution. The organic layer was separated, washed with dilute salt solution, dried (magnesium sulfate) and freed of solvent. An nmr spectrum of the solid residue, 4.1 g., showed it to contain mainly starting material (*ca.* 80%) based on the absorptions at -2.78 ($-SCH_3$) and -4.22 ($-OCH_3$) ppm (TMS). The reaction was repeated using this material, 0.67 g. (approx. equiv. amount) of sodium methoxide and 200 ml. of methanol; heating at 57° was continued for 64 hours. The reaction mixture was worked up as

before except that the initial bicarbonate layer was further basified with a little concentrated ammonia, extracted four times with methylene chloride, and these extracts were combined with the initial methylene chloride layer. There was obtained 3.5 g. of crude product which still contained considerable starting material, *ca.* 34%. This material was refluxed in 50 ml. of methanol with 0.30 g. of sodium methoxide for 17 hours, water and carbon dioxide excluded by a Drierite-Ascarite tube. Crude product, 3.2 g., was obtained as before. Recrystallization from methylene chloride-cyclohexane yielded 2.6 g. of dull, golden needles, m.p. 135-137.5°. This material still contained *ca.* 18% starting material.

(B) A solution of sodium methoxide, 0.31 g. (0.0135 g. atom) of sodium in 50 ml. of methanol, 3.7 g. (0.0135 mole) of 1-[(2-(dimethylamino)ethyl)amino[-4-(methylthio)pyridazino[4,5-*d*]-pyridazine and 1.0 ml. of dimethyl sulfoxide (b.p. 88°/25 mm.) was refluxed under nitrogen for 25 hours. The reaction mixture was treated with 0.95 ml. of acetic acid and evaporated *in vacuo* with the aid of a rotary evaporator, a vacuum pump was finally used to remove most of the unchanged dimethyl sulfoxide. Further workup was as previously. The crude product, 3.9 g., still contained some dimethyl sulfoxide, but only apparent traces of the starting material; thus, 3.85 g., was dissolved in 50 ml. of methylene chloride and filtered to remove a small amount of insoluble material. The filtrate was Darco treated, filtered and the new filtrate concentrated to *ca.* 8-10 ml. by warming whereupon five 20 ml. portions of cyclohexane were added with warming and swirling after each portion. The product crystallized as golden yellow needles, 2.65 g. (80%), m.p. 138.5-140.5°. Material (2.3 g.) of m.p. 140.5-142° was similarly obtained from the reaction of 2.55 g. of crude product (containing 18% starting material) and 0.110 g. of sodium methoxide in 40 ml. of methanol during 24 hours of reflux; infrared (Nujol): ν 3370 (N-H) cm^{-1}; nmr (deuteriochloroform): -2.32 (singlet, $-N(CH_3)_2$), -2.70 (triplet, $-CH_2-N$), -3.70 (triplet, $H-N-CH_2-$), -4.22 (singlet, $-OCH_3$), -6.58 (N-H, broad) and -9.72 and -9.83 (ring protons) ppm (TMS).

Anal. Calcd. for $C_{11}H_{16}N_6O$: C, 53.2; H, 6.50; N, 33.85. Found: C, 53.1; H, 6.57; N, 33.66.

1-[2-(Dimethylamino)ethoxy]-4-(dimethylamino)pyridazino[4,5-*d*]-pyridazine (VIIIc).

Under a nitrogen atmosphere were mixed with cooling and stirring 0.542 g. (0.0113 g. atom) of sodium hydride mineral oil dispersion (52.5% sodium hydride) and 35 ml. of redistilled 2-dimethylaminoethanol. When the release of hydrogen was complete, 2.5 g. (0.0113 mole) of 1-(dimethylamino)-4-(methylthio)-pyridazino[4,5-*d*]pyridazine (VIb) was added and the stirred mixture was heated briefly to 90° to effect solution, then at 50-55° for 7 hours. After standing overnight, 0.7 ml. (0.012 mole) of acetic acid was added and the solvent was removed *in vacuo* at a maximum temperature of 65°, a vacuum pump being used to remove final traces of solvent. The residue was triturated in 30 ml. of 0.5 *N* hydrochloric acid and concentrated hydrochloric acid was added dropwise to lower the *p*H to 5.5-6. This mixture was extracted with two 15-ml. portions of methylene chloride. The combined organic layers were evaporated to dryness, the residue was triturated in hot cyclohexane, filtered and recrystallized from 2-propanol to afford 0.4 g. of starting material, m.p. 158.5-159.5°. The aqueous layer was filtered then made basic, and nearly saturated, by addition of solid potassium carbonate. This was extracted four times with 50 ml. portions of methylene chloride and the combined extracts were dried (magnesium sulfate) and subsequently evaporated to yield 2.9 g. of crude material which after recrystallization from 75 ml. of cyclohexane afforded 1.45 g. (59%) of soft yellow crystals, m.p. 85-86°; ultraviolet: λ max (MeOH), 342 (log ϵ 7.71) mμ; nme (deuteriochloroform): -2.40 (singlet, $-CH_2-N(CH_3)_2$), -2.90 (triplet, $-CH_2-N$), -3.25 (singlet, $-N(CH_3)_2$), -4.76 (triplet, $-O-CH_2-$) and -9.81 (singlet, ring protons) ppm (TMS).

Anal. Calcd. for $C_{12}H_{18}N_6O$: C, 54.9; H, 6.92; N, 32.04. Found: C, 54.8; H, 7.14; N, 32.32.

Reaction of 1-Methoxy-4-(methylthio)pyridazino[4,5-*d*]pyridazine (VIIc) with Amines and Hydrazine.

(A) *N,N*-Dimethylethylenediamine.

One gram of 1-methoxy-4-(methylthio)pyridazino[4,5-*d*]pyridazine (containing 10 mole percent of the 1,4-dimethoxy derivative) and 10 ml. of *N,N*-dimethylethylenediamine were stirred and heated at 85-98° with exclusion of moisture and carbon dioxide (Drierite and Ascarite) for 1.25 hours. Unchanged amine was removed *in vacuo* at 55°. Toluene was added to the residue and the mixture evaporated again *in vacuo*. This step was repeated several times to remove residual amine. Examination of the solid residue (deuteriochloroform solution) showed it to consist essentially of 1-[(2-dimethylamino)ethyl]amino-4-(methylthio)pyridazino[4,5-*d*]pyridazine (VIa) and 1,4-dimethoxypyridazino[4,5-*d*]-pyridazine (IXc) *ca.* 92 and 8 (mole %), respectively.

(B) Dimethylamine.

1-Methoxy-4-(methylthio)pyridazino[4,5-*d*]pyridazine (same material used in preceding experiment) and 20 ml. of methanolic dimethylamine (3.1 *N*) were heated 15 hours in a closed pressure bottle. The reaction solution was evaporated *in vacuo* to dryness and the residue was analyzed by nmr (deuteriochloroform solution). The composition of the product mixture was (pyridazino[4,5-*d*]-pyridazine derivative and approximate mole % in parentheses): 1-(dimethylamino)-4-(methylthio)pyridazino[4,5-*d*]pyridazine (VIb) (56%), 1-(dimethylamino)-4-methoxypyridazino[4,5-*d*]pyridazine (VIIIa) (6%), 1-methoxy-4-(methylthio)pyridazino[4,5-*d*]-pyridazine (VIIc) (17%), and 1,4-dimethoxypyridazino[4,5-*d*]-pyridazine (IXc) (21%).

(C) Hydrazine.

A solution of 6.5 g. 1-methoxy-4-(methylthio)pyridazino-[4,5-*d*]pyridazine (containing 6 mole percent of the 1,4-dimethoxy-pyridazino[4,5-*d*]pyridazine), 3 ml. of hydrazine (95%) and 80 ml. of acetonitrile was refluxed for 30 minutes. The solid material which separated after standing 5 hours was collected on a filter, washed with acetonitrile and dried to 3.0 g. of brown solid. There was obtained two subsequent crops of 0.8 and 2.0 g. from the mother liquor on standing. The composition of the three crops was determined by nmr analysis in trifluoroacetic acid. After normalizing, the overall composition of the three crops corresponded to (pyridazino[4,5-*d*]pyridazine derivative and approx. mole % in parentheses): 1-hydrazino-4-(methylthio)pyridazino-[4,5-*d*]pyridazine (VIc) (77%), 1-hydrazino-4-methoxypyridazino-[4,5-*d*]pyridazine (5%) and 1-methoxy-4-(methylthio)pyridazino-[4,5-*d*]pyridazine (VIIc) (18%). Presence of 1-hydrazino-4-methoxypyridazino[4,5-*d*]pyridazine derivative was based on the absorption of the singlet at -4.58 ppm (from TMS) attributed to methoxyl. The methoxy group of 1-methoxy-4-(methylthio)-pyridazino[4,5-*d*]pyridazine absorbed at -4.48 (18).

1-[2-(Dimethylamino)ethoxy]-4-hydroxypyridazino[4,5-*d*]pyridazine (IXb).

To a solution of the sodium salt of dimethylaminoethanol (prepared as described previously from 0.77 g. (0.0158 mole) of 52.5% sodium hydride-mineral oil dispersion in 35 ml. of dimethylaminoethanol) was added 3.3 g. (0.015 mole) of 1-methoxy-4-(methylthio)pyridazino[4,5-*d*]pyridazine (96% pure). This mixture was stirred and heated under nitrogen, solution

resulting at 30°. After 6 hours at 68-75°, a thick, gelatinous material had separated. The reaction was cooled, quenched with 0.9 ml. of acetic acid, and freed of solvent amine *in vacuo*. The residue was triturated with 50 ml. of *N* hydrochloric acid, additional 5 *N* hydrochloric acid was used to lower the *p*H to *ca.* 1.5. The mixture was extracted with methylene chloride. The aqueous layer was treated with Darco and Celite, filtered and the filtrate was treated with solid potassium carbonate until a permanent turbidity remained. This mixture was extracted with methylene chloride (5 x 50 ml.) and the combined extracts were dried (magnesium sulfate) and evaporated. The residue was subjected to a mechanical pump vacuum and a temperature of 50° to remove traces of dimethylaminoethanol. Obtained 3.7 g. of semisolid which was recrystallized from 40 ml. of benzene (Darco used) to produce 0.66 g. (19%) of soft, light yellow crystals of 1-[2-(dimethylamino)ethoxy]-4-hydroxypyridazino[4,5-*d*]pyridazine m.p. 163.5-165° and 168.5-169.5° after recrystallization from benzene. infrared (Nujol): ν, 1700 (keto tautomer carbonyl) cm^{-1}; nmr (deuteriochloroform): -2.49 (singlet, $-N(CH_3)_2$), -2.96 (triplet, $-CH_2-N$), -4.63 (triplet, $-OCH_2-$), and -9.73 and -9.97 (singlets, ring protons) ppm (TMS). The hydroxy amido proton was not located.

Anal. Calcd. for $C_{10}H_{13}N_5O_2$: C, 51.1; H, 5.57; N, 29.77. Found: C, 51.3; H, 5.79; N, 30.06.

Evaporation of the benzene mother liquor left a residue of 1.6 (~35%) g., a light red-brown oil whose nmr spectrum showed it to be principally 1,4-bis-[2-(dimethylamino)ethoxy]pyridazino[4,5-*d*]-pyridazine (IXa). There were no absorption bands attributable to 1-[2-(dimethylamino)ethoxy]-4-methoxypyridazino[4,5-*d*]pyridazine, the intended product of this reaction.

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REFERENCES

(1) H. Keller and H. von Halbau, *Helv. Chim. Acta*, 27, 1253 (1944).

(2) R. G. Jones, *J. Am. Chem. Soc.*, 78, 159 (1956).

(3) J. K. Stille and R. Ertz, *ibid.*, 86, 661 (1964).

(4) There is strong evidence that the 5,8-dimethyl-9,10-dihydropyridazino[4,5-*d*]pyridazine-1,4-diol as reported by R. Seka and H. Preissecker (*Monatsh. Chem.*, 57, 81 (1931)) and by C. Bulow (*Ber.*, 37, 91 (1904)) is a bipyrazole, 3,3′-dimethyl-5,5′-dioxo-4,4′-dipyrazolinyl, see references 2 and 6.

(5) It is interesting to note that a similar isomeric system, viz., pyrazino[2,3-*d*]pyridazine and some of its derivatives were reported recently, N. R. Patel and R. N. Castle, *J. Heterocyclic Chem.*, 3, 512 (1967).

(6a) W. L. Mosby, *J. Chem. Soc.*, 3997 (1957); (b) T. Curtius, *J. Prakt. Chem.*, 50, 508 (1894).

(7) L. Fieser, "Experiments in Organic Chemistry", D. C. Heath and Co., Boston, Mass., 1955, p. 199.

(8) E. A. Steck, R. P. Brundage and L. T. Fletcher, *J. Am. Chem. Soc.*, 76, 4454 (1954).

(9) R. D. Haworth and S. Robinson, *J. Chem. Soc.*, 777 (1948).

(10) A. Albert, D. J. Brown and H. C. S. Wood, *ibid.*, 3832 (1954).

(11) J. H. M. Hill and J. G. Krause, *J. Org. Chem.*, 29, 1642 (1964).

(12) J. Hine, "Physical Organic Chemistry", McGraw-Hill Book Company, Inc., New York, N. Y., 1956, p. 72.

(13) P. Coad, R. A. Coad, and J. Hypock, *J. Org. Chem.*, 29, 1751 (1964).

(14) G. S. Hammond and M. F. Hawthorne in "Steric Effects in Organic Chemistry", M. S. Newman, Ed., John Wiley and Sons, Inc., New York, N. Y., 1956, pp. 172-176.

(15) R. G. Jones and K. C. McLaughlin, in "Organic Synthesis", Coll. Vol. IV, N. Rabjohn, Ed., John Wiley and Sons, Inc., New York, N. Y., 1963, p. 824.

(16) Professor R. Castle and his group at the University of New Mexico have isolated and characterized free 1,4-dithiopyridazino-[4,5-*d*]pyridazine. Private communication.

(17) E. Tauber, *Ber.*, 28, 451 (1895).

(18) Note that the methoxyl of the hydrazine derivative should absorb further downfield than the methoxyl of either 1-methoxy-4-(methylthio)pyridazino[4,5-*d*]pyridazine or 1,4-dimethoxypyridazino[4,5-*d*]pyridazine in trifluoroacetic acid because of the protonated hydrazino function which exerts a stronger deshielding effect than either methylthio or methoxyl functions.

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