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Synthesis of Substituted Pyridazino[4,5-*c*]pyridazines

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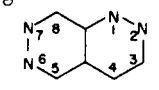
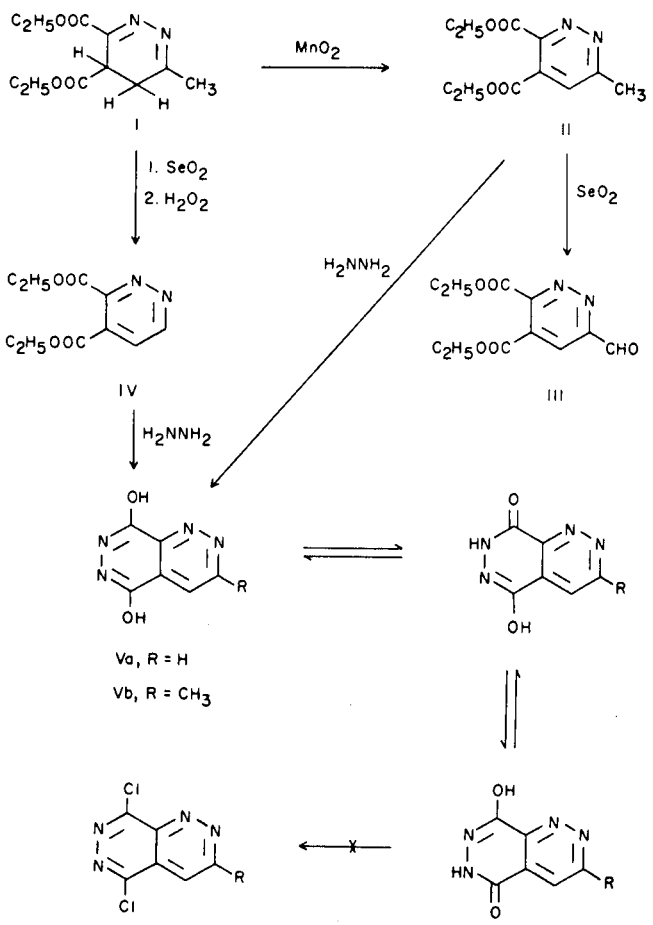
Several pyridazino[4,5-*c*]pyridazines substituted in the 5- and 8-positions with hydroxyl, mercapto and amino groups and in the 3-position with a methyl group or a hydrogen atom have been prepared. In the course of this work five previously unreported pyridazine derivatives have also been synthesized.

The only reported derivative of pyridazino[4,5-*c*]pyridazine is the compound described by Gault, *et al.*, (1) namely 4,4a,6,7(2*H*)-tetrahydropyridazino[4,5-*c*]pyridazine-3,5,8-trione. Since unsubstituted pyridazino[4,5-*c*]-pyridazine has also not been described in the literature, the chemistry of this system has been essentially unexplored. We therefore began a study of this ring system, first, to study the fundamental chemistry, and second, because of its relationship to the cinnoline, phthalazine, and pteridine systems.

Our approach to the preparation of the pyridazino-[4,5-*c*]pyridazine ring system was by the interaction of hydrazine with either diethyl 6-methylpyridazine-3,4-dicarboxylate (II) or diethyl pyridazine-3,4-dicarboxylate (IV) to give 3-methyl-5,8-dihydroxypyridazino[4,5-*c*]pyridazine (Vb) or 5,8-dihydroxypyridazino[4,5-*c*]pyridazine (Va), respectively. We had then hoped to be able to replace the hydroxyl groups of Va and Vb with chlorine atoms, which should undergo nucleophilic displacement easily and therefore provide a pathway to obtain pyridazino[4,5-*c*]pyridazines substituted in the 5- and 8-positions with a variety of groups such as alkyl, alkoxy, aryloxy, alkylamino, and others. Unfortunately, none of the usual chlorinating procedures were successful in converting Va or Vb to their dichloro derivatives. Treatment of Va or Vb with refluxing phosphorus oxychloride led either to recovery of starting material or to its decomposition depending upon reaction time. Treatment of Va or Vb with a refluxing mixture of phosphorus oxychloride and phosphorus pentachloride according to the procedure of Armarego, (2) who successfully converted the similar 5,8-dihydroxypyrido[2,3-*d*]-pyridazine to its dichloro derivative, led only to decomposition and to the isolation of small amounts of solid materials. These products displayed a broad melting range and showed new infrared carbonyl stretching bands at 1690-1700 cm^{-1}, whereas the carbonyl stretching bands of Va and Vb appear at 1665-1670 cm^{-1}. Since a band at 1690-1700 cm^{-1} may be assigned to an amide substituted with an aromatic group on the nitrogen atom (3), the frequency shift from 1665-1670 to 1690-1700 cm^{-1} may be interpreted that the desired replacement of the hydroxyl with the chloro group did occur at least partially, but that a chlorinated molecule then alkylated a second unreacted molecule of Va or Vb to give a cyclic amide substituted on the nitrogen atom. An example of just such



Pyridazino[4,5-*c*]pyridazine (12)



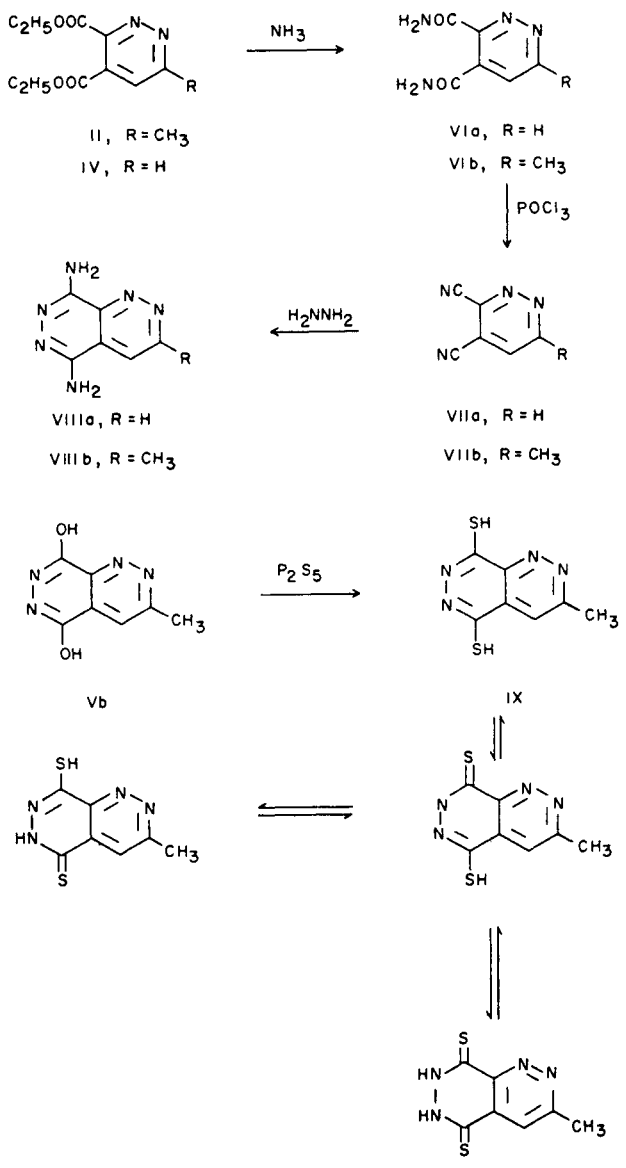
a side-reaction in the chlorination of 1(2*H*)-phthalazinone with the same shift in the carbonyl stretching frequency was reported by Castle and Takano (4). Treatment of Va or Vb with a mixture of phosphorus oxychloride and *N,N*-dimethylaniline according to the procedure of Nitta, *et al.*, (5) led to decomposition and small amounts of ill-defined solids, or to partial recovery of starting material depending upon the reaction time. Similar results were observed when Va and Vb was heated under pressure at 140° with phosphorus pentachloride according to the procedure of Hirsh and Orphanos (6).

Jones (7), who first prepared II, was able to obtain this compound in 37% yield by the oxidation of diethyl 6-methyl-4,5-dihydropyridazine-3,4-dicarboxylate (I) with potassium permanganate in acetone. We have found that I may be converted to II in 79% yield by employing manganese dioxide in acetone as the oxidizing agent. Compound II could then be oxidized by selenium dioxide to the previously unreported diethyl 6-formylpyridazine-3,4-dicarboxylate (III), while under more stringent conditions using selenium dioxide followed by hydrogen peroxide and heat, compound I could be aromatized and decarboxylated in one step to give diethyl pyridazine-3,4-dicarboxylate (IV) in good yield. A third previously unreported pyridazine derivative, pyridazine-3,4-dicarboxamide (VIa), was then prepared by treatment of IV with methanolic ammonia. Compound VIa was converted in good yield to pyridazine-3,4-dinitrile (VIIa) by treatment with phosphorus oxychloride, and 6-methylpyridazine-3,4-dicarboxamide (VIb) was converted to 6-methylpyridazine-3,4-dinitrile (VIIb) in the same manner. Both VIIa and VIIb, which are new pyridazine derivatives, which were subsequently caused to interact with hydrazine in methanol or ethanol to give 5,8-diaminopyridazino[4,5-c]pyridazine (VIIIa) and 3-methyl-5,8-diaminopyridazino[4,5-c]pyridazine (VIIIb), respectively. It was necessary to obtain compounds VIIIa and VIIIb in this manner because of our inability to convert Va and Vb to their dichloro derivatives, which in our original plan we had hoped to transform to VIIIa and VIIIb.

When II was allowed to interact with hydrazine in methanol to give Vb, immediate gel formation occurred which precluded efficient stirring and refluxing of the reaction mixture. Gel formation was avoided by inclusion of a small amount of water in the solvent.

The infrared spectrum of dinitrile (VIIa) displayed two sharp, weak absorptions at 2255 and 2025 cm^{-1}, both of which may be assigned to the nitrile stretching vibration, while the dinitrile (VIIb) showed only one very weak, broad absorption band at 2250 cm^{-1}, also assignable to the nitrile stretching vibration. Such diminution in intensity of this normally strong band has been reported previously when electron-withdrawing groups are adjacent to the carbon atom which bears the nitrile group (8,9).

The preparation of 3-methyl-5,8-dimercaptopyridazino[4,5-c]pyridazine (IX) by the interaction of Vb with phosphorus pentasulfide was found to be sensitive to reaction conditions. Thus, when phosphorus pentasulfide was added to Vb in pyridine at room temperature, heated briefly to boiling, and then stirred at room temperature for 12 hours there was obtained a yellow-brown material, m.p. 149-151° (dec.) which analyzed for only 11.65% carbon and 6.81% nitrogen instead of the expected values of 39.98% and 26.65%, respectively. When phosphorus pentasulfide was added portionwise to a boiling solution of Vb in pyridine and the mixture was then refluxed for 1 hour, the dimercapto compound (IX) was obtained in good yield. A strong carbonyl stretching absorption at 1665 cm^{-1} is present in the infrared spectrum of Vb. This band is absent, as would be expected, from the spectrum of IX.



EXPERIMENTAL

Melting points were determined in a Thomas-Hoover capillary melting point apparatus, and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 337 spectrophotometer with the exception of the spectrum of compound VIIa, which was recorded on the Perkin-Elmer 237B instrument. Infrared band intensities are designated by the abbreviations, s (strong), m (medium), w (weak). Ultraviolet spectra were determined on the Bausch and Lomb Spectronic 505 spectrophotometer, and NMR spectra were recorded on the Varian A-60A instrument. The NMR spectra were compared with tetramethylsilane as an internal standard when chloroform-d_1 was used as the solvent, with sodium 3-(trimethylsilyl)propanesulfonate as an internal standard when deuterium oxide was used as the solvent, and with the residual protons of dimethylsulfoxide-d_6 placed at 2.5 δ as an internal standard when dimethylsulfoxide-d_6 was used as the solvent.

Diethyl 6-Methyl-4,5-dihydropyridazine-3,4-dicarboxylate (I).

This compound was prepared according to the procedure of Jones (7) from the interaction of ethyl 2-ethoxalyl-4-ketovalerate with hydrazine in 95% ethanol.

Diethyl 6-Methylpyridazine-3,4-dicarboxylate (II).

Diethyl 6-methyl-4,5-dihydropyridazine-3,4-dicarboxylate (1.0 g., 0.00416 mole) was dissolved in 100 ml. of acetone, and to it was added 10.0 g. of manganese dioxide which had been prepared according to the method of Yoshida and Kubota (10). The reaction mixture was stirred magnetically at room temperature for 24 hours; manganese dioxide was removed from it by suction filtration, and the acetone was evaporated under reduced pressure on a hot water bath to give 0.98 g. of yellow oily II, which solidified after standing for several hours at room temperature. After recrystallization from a mixture of 60-90° ligroin and ether, there was obtained 0.78 g. (79%) of II, long white needles, m.p. 53.0-54.0°. The reported melting point for this compound is 53-53.5° (7); NMR spectrum (deuteriochloroform) 7.74 δ (C_5-H, singlet), 4.46 δ (ethyl-CH_2-, two nearly superimposed quartets), 2.85 δ (C_6-CH_3, singlet), 1.42 δ (ethyl-CH_3, two nearly superimposed triplets).

Diethyl 6-Formylpyridazine-3,4-dicarboxylate (III).

Diethyl 6-methylpyridazine-3,4-dicarboxylate (0.48 g., 0.002 mole) was dissolved in 10 ml. of 1,4-dioxane, which had been freshly purified by passage through a column of alumina. The solution was stirred magnetically at room temperature, and to it was added portionwise 0.30 g. (0.0027 mole) of selenium dioxide (K & K Laboratories, Inc.). The mixture was stirred and heated under reflux 30 minutes and 1,4-dioxane was removed by evaporation under reduced pressure on a hot water bath. Chloroform was added to the residue; the solution was filtered with suction to remove selenium metal, and the chloroform filtrate was washed once with water in a separatory funnel. The chloroform solution was dried over anhydrous magnesium sulfate; magnesium sulfate was removed by filtration, and chloroform was evaporated from the filtrate and replaced with commercial absolute ethanol. To the ethanolic solution was added 1.0 g. of silver metal which had been freshly precipitated by the interaction of zinc and aqueous silver nitrate. The mixture was stirred magnetically at room temperature overnight and a grey-brown mixture of silver and silver selenide was removed by suction filtration. Ethanol was evaporated from the filtrate *in vacuo* on a hot water bath and the residue was subjected to chromatography through a 38 x 1.5 cm. column of silica gel (E. Merck, 0.05-0.20 mm.) using benzene as the first eluent. Upon evaporation of benzene from the filtrate, there was obtained 0.20 g. (40%) of light yellow oily III. The column was then eluted using benzene-1.5% ethanol as eluent to give 0.17 g. of a light orange oily mixture which was shown by NMR analysis to consist of compounds II, III, and IV in a ratio of 4.1:1.0:1.4. An analytical sample of III was obtained by distillation of III in a micro-distillation assembly under nitrogen at 0.2 mm. and an oil-bath temperature of 170°. Much decomposition accompanied distillation. Compound III was thus obtained as a light yellow oil; U. V. λ max. (95% ethanol), 208 (ϵ, 18,570), 252 mμ (ϵ, 2,040); infrared cm^{-1}, 3065 (w), 2985 (m), 2935 (w), 2900 (w), 2860 (w), 1745 (s), 1635 (w), 1575 (w), 1535 (w), 1465 (m), 1445 (m), 1415 (w), 1380 (m), 1300 (w), 1285 (s), 1190 (s), 1154 (s), 1110 (m), 1084 (s), 1020 (s), 950 (m), 930 (w), 860-850 (m), 825 (w), 805 (w), 784 (w), 764 (m), 700 (m), 683 (m), (liquid film on sodium chloride plates); NMR spectrum (deuteriochloroform), 10.48 δ (C_6-CHO, singlet), 8.43 δ (C_5-H, singlet), 4.53 δ (ethyl-CH_2-, two nearly superimposed quartets), 1.45 δ (ethyl-CH_3, two nearly superimposed triplets).

Anal. Calcd. for $C_{11}H_{12}N_2O_5$: C, 52.38; H, 4.80; N, 11.11. Found: C, 52.35; H, 4.99; N, 11.03.

Compound III formed a 2,4-dinitrophenylhydrazone derivative, yellow needles, m.p. 200-201°, from 95% ethanol.

Anal. Calcd. for $C_{17}H_{16}N_6O_8$: C, 47.22; H, 3.73; N, 19.44. Found: C, 47.30; H, 3.80; N, 19.70.

Diethyl Pyridazine-3,4-dicarboxylate (IV).

A solution of diethyl 6-methyl-4,5-dihydropyridazine-3,4-dicarboxylate (2.40 g., 0.01 mole) and 50 ml. of 1,4-dioxane was stirred magnetically at room temperature and to it was added portionwise 3.33 g. (0.03 mole) of selenium dioxide. The mixture was stirred for one hour at room temperature, during which time a red solid was precipitated. The mixture was then heated under reflux and stirred for one additional hour. 1,4-Dioxane was removed by evaporation under reduced pressure on a hot water bath and 50 ml. of water was added to the residue. The aqueous mixture was extracted with chloroform. The chloroform extract was dried over anhydrous magnesium sulfate and the magnesium sulfate was removed by filtration. Chloroform was evaporated from the filtrate to give a black, viscous residue. Examination of this residue by NMR spectrometry indicated that all of the starting material had been consumed, and that the residue was mainly a mixture of diethyl pyridazine-3,4-dicarboxylate and diethyl 6-formylpyridazine-3,4-dicarboxylate in a 1:1 ratio. The residue was dissolved in 50 ml. of acetone, and to it was added 0.01 mole (1.13 g. of 30% aqueous solution) of hydrogen peroxide. The solution was heated under reflux for 45 minutes, acetone was evaporated from it, and the residue was heated in an oil bath at 130-135° for 25minutes. After allowing the residue to cool to room temperature, 50 ml. of water was added to it, and the mixture was extracted with chloroform. The chloroform extract was dried over anhydrous magnesium sulfate, and the magnesium sulfate was removed by filtration. Chloroform was evaporated from the filtrate and the residue was subjected to distillation at 0.1 mm. of mercury over a broad temperature range until a solid, red contaminant began to codistil with the product. There was obtained 1.86 g. (83%) of crude IV. Examination of the distillate by NMR spectrometry indicated that it consisted almost entirely of compound IV. This material was further purified by elution through a short (1 x 10 cm.) column of alumina (Woelm, neutral, activity grade I) using benzene-5% ethanol as eluent, followed by a second distillation at 117-119° and 0.05 mm. to give IV as a light yellow oil; U. V. λ max (95% ethanol), 210 (ϵ, 7,770), 261 (ϵ, 1,430), 330 mμ (ϵ, 210); infrared cm^{-1}, 2990 (m), 1740 (s), 1570 (w), 1550 (w), 1470 (m), 1445 (m), 1370 (m), 1300 (s), 1190 (s), 1154 (m), 1120 (m), 1100 (s), 1030 (m), 860 (w), 810 (w), 760 (m), 720 (w), (liquid film on potassium bromide plates); NMR spectrum

(deuteriochloroform), 9.51 δ (C_6-H, doublet), 8.00 δ (C_5-H, doublet), 4.50 δ (ethyl-CH_2-, two nearly superimposed quartets), 1.43 δ (ethyl-CH_3, two nearly superimposed triplets).

Anal. Calcd. for $C_{10}H_{12}N_2O_4$: C, 53.57; H, 5.39; N, 12.49. Found: C, 53.77; H, 5.50; N, 12.17.

5,8-Dihydroxypyridazino[4,5-c]pyridazine (Va).

In a procedure similar to that employed by Carbon (11) for the interaction of diethyl imidazoledicarboxylates with hydrazine, a solution of diethyl pyridazine-3,4-dicarboxylate (2.2 g., 0.00981 mole) and 25 ml. of methanol was stirred magnetically at room temperature, and to it was added dropwise a solution of 0.3 mole of hydrazine (0.99 g. of 97% hydrazine in water), 2.0 ml. of water and 5.0 ml. of methanol. The reaction mixture was stirred and heated under reflux for one hour, and then allowed to stand at room temperature overnight to complete precipitation of the orange hydrazinium salt of Va. The salt was removed from the reaction mixture by suction filtration, washed with methanol, and allowed to air-dry. The salt was then dissolved in 35 ml. of water; the solution was heated to 80°, made acidic to Congo Red test paper by the dropwise addition of concentrated hydrochloric acid, and then stirred and heated at 80-85° for 15 minutes. After the solution was allowed to cool to room temperature, a yellow solid was removed from it by suction filtration, washed with water and allowed to air-dry to give 1.38 g. (86%) of bright yellow microcrystalline Va, which was further purified by recrystallization from water to yield Va as its monohydrate, which darkens at 315° and decomposes at 336-338°; U. V. λ max. (water), 202 (ε, 25,900), 260 (ε, 3,250), 335 mμ (ε, 2,750); infrared cm^{-1}, 3600-2700 broad envelope (m), 1670 (s), 1580 (m), 1500 (m), 1475 (m), 1390 (w), 1320 (m), 1225 (m), 1190 (m), 1080 (m), 1040 (m), 940 (w), 890 (m), 860 (w), 830 (w), 815 (w), 784 (m), 725 (w), 640 (w), 575 (w), 490 (m), (potassium bromide).

Anal. Calcd. for $C_6H_4N_4O_2 \cdot H_2O$: C, 39.56; H, 3.32; N, 30.76. Found: C, 39.84; H, 3.24; N, 31.10.

When Va was purified by sublimation at 240-295° and 0.01 mm., it was obtained in anhydrous form.

Anal. Calcd. for $C_6H_4N_4O_2$: C, 43.91; H, 2.46; N, 34.14. Found: C, 43.94; H, 2.81; N, 33.83.

3-Methyl-5,8-dihydroxypyridazino[4,5-c]pyridazine (Vb).

A solution of diethyl 6-methylpyridazine-3,4-dicarboxylate (2.34 g., 0.00982 mole) and 25 ml. of methanol was stirred magnetically at room temperature, and to it was added dropwise a solution of 0.3 mole of hydrazine (0.99 g. of 97% hydrazine in water), 2.0 ml. of water, and 5.0 ml. of methanol. After completion of addition, the mixture was stirred magnetically and heated under reflux for one hour, allowed to cool to room temperature, and 1.21 g. of an orange-red precipitate of the hydrazinium salt of Vb was removed from the mixture by suction filtration. The methanolic filtrate formed an orange gel after standing overnight at room temperature. This gel was partially broken up mechanically and filtered with suction to yield an additional 0.39 g. of Vb hydrazinium salt. The salt was dissolved in 50 ml. of water; the solution was heated to 80° and rendered acidic to Congo Red test paper by the dropwise addition of hydrochloric acid. After acidification the mixture was stirred and heated at 80° for 10 minutes and then was kept at 0° for several hours to deposit a yellow solid which was isolated by suction filtration, washed with water and allowed to air-dry to give 1.28 g. (73.1%) of yellow microcrystalline Vb, 270-274° (dec.) from water or by sublimation at 190° and 0.01 mm.; U. V. λ max. (water), 202 (ε, 27,760), 267 (ε, 3,410), 335 mμ (ε, 2,630); infrared cm^{-1}, 3700-3350 broad envelope (m), 3030 broad (s), 2870 broad (s), 1665 (s), 1585 (m), 1540 (w), 1480 (m), 1420 (m), 1400 (m), 1355 (w), 1310 (m), 1290 (m), 1240 (m), 1195 (m), 1130 (w), 1110 (w), 1090 (m), 1045 (w), 920 (w), 880 (w), 800 (m), 735 (m), 705 (w), 670 (w), 630 (w), 540 (m), 495 (m), 470 (w), (potassium bromide); NMR spectrum (dimethylsulfoxide-d_6), 8.03 δ (C_4-H, singlet), 4.80 δ (C_5-OH and C_8-OH, barely distinguishable from base line at room temperature, but sharpens and rises to a clearly visible broad singlet at 150°), 2.85 δ (C_3-CH_3, singlet).

Anal. Calcd. for $C_7H_6N_4O_2$: C, 47.19; H, 3.40; N, 31.45. Found: C, 47.09; H, 3.32; N, 31.17.

Pyridazine-3,4-dicarboxamide (VIa).

Diethyl pyridazine-3,4-dicarboxylate (6.42 g., 0.0286 mole) was dissolved in 100 ml. of anhydrous methanol, and the solution was saturated with gaseous ammonia. The reaction flask was stoppered, and the mixture allowed to stand overnight at room temperature. A white precipitate was isolated by suction filtration, washed with methanol, and allowed to air-dry to give 4.02 g. (85%) of VIa, white solid, m.p. 220-221°, after purification by sublimation at 190-200° and 0.01 mm.

Anal. Calcd. for $C_6H_6N_4O_2$: C, 43.38; H, 3.64; N, 33.72. Found: C, 43.41; H, 3.61; N, 33.55.

When VIa was purified by recrystallization from methanol containing a small amount of water, its monohydrate was obtained, m.p. 221-222°.

Anal. Calcd. for $C_6H_6N_4O_2 \cdot H_2O$: C, 39.13; H, 4.38; N, 30.43. Found: C, 39.08; H, 4.53; N, 30.06.

6-Methylpyridazine-3,4-dicarboxamide (VIb).

A solution of diethyl 6-methylpyridazine-3,4-dicarboxylate (8.41 g., 0.0353 mole) and 50 ml. of anhydrous methanol was saturated with gaseous ammonia and the mixture was processed in the manner described for compound VIa to give 5.27 g. (83%) of VIb, white solid, m.p. 244.5-245.5° after sublimation at 185-190° and 0.01 mm. The reported melting point for this compound is 245-246° from aqueous alcohol (7).

Anal. Calcd. for $C_7H_8N_4O_2$: C, 46.66; H, 4.48; N, 31.10. Found: C, 46.36; H, 4.47; N, 31.32.

3,4-Dicyanopyridazine (VIIa).

A mixture of pyridazine-3,4-dicarboxamide monohydrate (2.70 g., 0.01466 mole) and 50 ml. of phosphorus oxychloride was stirred magnetically at room temperature for 3.5 hours and was then stirred and heated under reflux in an oil bath for 1.25 hours. Excess phosphorus oxychloride was then removed by distillation under reduced pressure (20 mm.), and the reaction flask, containing a dark residue, was kept overnight in an evacuated desiccator containing potassium hydroxide pellets. The reaction flask was chilled thoroughly in an ice-salt bath; ice-water was added to its contents, and the mixture was gently shaken until the residue dissolved. The aqueous solution was made basic by the addition of ice-cold saturated aqueous sodium carbonate while the reaction flask was kept cold by immersion in an ice-salt bath. The basic solution was immediately extracted with 5 x 120 ml. of ether, and the ethereal extract was dried over anhydrous magnesium sulfate. The magnesium sulfate was removed by filtration, and the ether was evaporated to give a purple residue which solidified after standing for one hour at room temperature. This residue was subjected to sublimation at 55° and 0.01 mm. for 16 hours to give 1.4 g. (73%) of light yellow VIIa, m.p. 61-62.5°; U. V. λ max (95% ethanol), 206 (ε, 16,240), 225, shoulder (ε, 7,950), 271 mμ (ε, 740); infrared $cm.^{-1}$, 3130, (m), 3075 (s), 3050 (m), 2950 (w), 2255 (w), 2025 (w), 1900 (w), 1775 (w), 1730 (w), 1695 (w), 1560 (m), 1535 (m), 1425 (m), 1350 (s), 1300 (w), 1255 (w), 1245 (w), 1160 (w), 1100 (w), 1050 (w), 1030 (s), 1015 (w), 940 (w), 900 (s), 855 (m), 870 (w), 775 (m), 730 (m), (potassium bromide); NMR spectrum (deuteriochloroform); 9.76 δ (C_6-H, doublet),

8.15 δ (C_5-H, doublet).

Anal. Calcd. for $C_6H_2N_4$: C, 55.38; H, 1.55; N, 43.07. Found: C, 55.65; H, 1.68; N, 43.26.

3,4-Dicyano-6-methylpyridazine (VIIb).

A mixture of 6-methylpyridazine-3,4-dicarboxamide (2.0 g., 0.0111 mole) and 35 ml. of phosphorus oxychloride was stirred magnetically at room temperature for 3 hours, stirred and heated under reflux for one additional hour, and phosphorus oxychloride was removed from it by distillation under reduced pressure (20 mm.). The reaction flask, containing a black residue, was kept overnight in an evacuated desiccator containing potassium hydroxide pellets. The reaction flask was chilled thoroughly in an ice-salt bath; ice-water was added to its contents, and the mixture was agitated until the residue dissolved. The mixture was made basic by the addition of ice-cold saturated sodium carbonate while the reaction flask was kept cold in an ice-salt bath, and it was then extracted with a mixture of ether and 60-90° ligroin. The use of ether alone in this extraction step resulted in a heavy emulsion. The organic extract was dried over anhydrous magnesium sulfate; magnesium sulfate was removed by filtration, and the solvent was evaporated on a hot water bath *in vacuo* to give 0.74 g. (46%) of crude VIIb which solidified upon standing, white solid, m.p. 83-84.5° after sublimation at 50-60° and 0.05 mm. Compound VIIb may also be recrystallized from a mixture of ether and 60-90° ligroin in the form of long, very light yellow needles, which become gold colored after standing at room temperature overnight; U. V. λ max (95% ethanol), 209 (ε, 21,200), 228, shoulder (ε, 9,280), 279 mμ (ε, 1,250); infrared cm^{-1}, 3170 (w), 3075 (s), 2250 (w), 1585 (s), 1525 (w), 1400 (s), 1350 (w), 1230 (m), 1150 (w), 1130 (w), 1120 (m), 1050 (m), 945 (m), 920 (m), 763 (m), 739 (m), 721 (w), 625 (w), 525 (m), 460 (w), potassium bromide); NMR spectrum (deuteriochloroform), 7.88 δ (C_5-H, singlet), 3.00 δ (C_6-CH_3, singlet).

Anal. Calcd. for $C_7H_4N_4$: C, 58.33; H, 2.80; N, 38.88. Found: C, 58.60; H, 2.74; N, 38.93.

5,8-Diaminopyridazino[4,5-c]pyridazine (VIIIa).

A solution of 3,4-dicyanopyridazine (0.26 g., 0.002 mole) and 30 ml. of methanol was cooled to -10°, and to it was added portionwise with swirling over 30 minutes a similarly cooled solution of 0.004 mole of hydrazine (0.13 g. of 97% hydrazine in water) and 10 ml. of methanol. The mixture was allowed to remain at -10° for 4 hours after completion of addition, and then at room temperature overnight to give a deep red solution with a thin coating of a black solid deposited on the wall of the vessel. The methanolic solution was separated from the black solid by filtration and the black solid was discarded. Methanol was evaporated from the solution under reduced pressure (20 mm.) on a hot water bath and the brown solid residue was subjected to high vacuum (0.01 mm.) to remove all excess hydrazine. Methanol (30 ml.) was added to the residue and the solution was allowed to stand at room temperature for 24 hours, to deposit 0.1 g. of a dark brown solid (fraction I) which was isolated by filtration. Fraction I was set aside for later examination. Methanol was removed from the filtrate and replaced with benzene by boiling the methanolic solution and gradually replacing the evaporating methanol with benzene. The benzene solution was allowed to stand overnight to precipitate 0.05 g. of orange-brown solid VIIIa, which was isolated by filtration. The benzene filtrate was boiled, and 60-90° ligroin was added to it until most of the benzene had been replaced with ligroin, which caused the precipitation of 0.12 g. additional orange solid VIIIa. Brown solid fraction I was treated with boiling methanol, and the methanol-insoluble portion was removed by filtration and discarded. Methanol was replaced in the filtrate by 60-90° ligroin as described above to precipitate an additional 0.02 g. of VIIIa. There was thus obtained a total of 0.19 g. (59%) of VIIIa, which was further purified by dissolution in methanol followed by successive replacement of the boiling methanol with benzene and 60-90° ligroin as previously described to give the product as an orange solid which shrinks at 165° and then gradually turns black and decomposes, but does not melt, up to 360° where observation of its melting point behavior was discontinued; U. V. λ max (water), end absorption 197 (ε, 24,650), 214, shoulder (ε, 15,500), 260 (ε, 5,290), 338 mμ (ε, 5,200); infrared cm^{-1}, 3600-2700 broad envelope (s), 1660 (s), 1625 (s), 1585 (s), 1535 (m), 1450 (m), 1360 (m), 1330 (w), 1210 (w), 1170 (w), 1060 (w), 1000 (w), 860 (w), 780 (w), (potassium bromide); NMR spectrum (deuterium oxide), 9.66 δ (C_3-H, doublet), 8.12 δ (C_4-H, doublet).

Anal. Calcd. for $C_6H_6N_6$: C, 44.44; H, 3.73; N, 51.83. Found: C, 44.50; H, 4.03; N, 51.42.

3-Methyl-5,8-diaminopyridazino[4,5-c]pyridazine (VIIIb).

To a solution of 0.12 g. (0.000833 mole) 3,4-dicyano-6-methylpyridazine and 15 ml. of 95% ethanol at -10° was added slowly and intermittently a similarly cooled solution of 0.5 ml. of 97% hydrazine and 5 ml. of 95% ethanol, keeping the temperature of the reaction mixture always near -10°. After completion of addition, the reaction mixture was allowed to remain at -10° overnight to give a red-black solution from which ethanol and excess hydrazine were then removed under reduced pressure first on a hot water bath at 20 mm. and finally at 0.01 mm. to give 0.1 g. of a black, solid residue. The residue was eluted through a column of silica gel (E. Merck, 0.05-0.20 mm). using commercial absolute ethanol to give VIIIb as an orange solid which was further purified by dissolution in methanol, filtration, and replacement of the methanol from the filtrate with benzene by boiling the methanolic solution and gradually replacing the evaporating methanol with benzene. Compound VIIIb was obtained by deposition from the benzene as an orange powder which became red at 164° and then gradually blackens and decomposes as the temperature is raised. No definite melting point was observed; U. V. λ max (95% ethanol), 206 (ε, 16,850), 227, shoulder (ε, 12,140), 273 (ε, 2,950), 350 mμ (ε, 1,970); infrared cm^{-1}, 3700-2700 (s), 1675 (m), 1625 (s), 1530 (m), 1460 (m), 1385 (w), 1360 (w), 1310 (w), 1260 (w), 1220-1190 (m), 1050 (m), 840 (w), 805 (w), 740 (w), 700 (w), 535 (w), 495 (w), (potassium bromide); NMR spectrum (deuterium oxide), 7.77 δ (C_4-H, singlet), 2.87 δ (C_3-CH_3, singlet).

Anal. Calcd. for $C_7H_6N_6$: C, 47.72; H, 4.58; N, 47.71. Found: C, 47.84; H, 4.76; N, 47.60.

3-Methylpyridazino[4,5-c]pyridazine-5,8-dithione (IX) (13).

A solution of 3-methyl-5,8-dihydroxypyridazino[4,5-c]pyridazine (0.50 g., 0.0028 mole) and 30 ml. of freshly distilled, anhydrous pyridine was stirred magnetically and heated until it began to reflux vigorously. Phosphorus pentasulfide (1.33 g., 0.006 mole) was then added slowly, portionwise, causing the reaction mixture to turn in color from yellow to black. After completion of addition the mixture was stirred and heated under reflux for one hour and pyridine was then removed from it by distillation under reduced pressure (20 mm.). The residue was chilled in an ice bath and to it was added about 40 ml. of ice-water. The aqueous mixture was heated on a steam bath for one hour and then filtered with suction while hot. After allowing the filtrate to cool to room temperature, it was acidified to Congo Red test paper by addition of concentrated hydrochloric acid to cause precipitation of a brown solid material. This solid was isolated by suction filtration, washed with water, and was then taken up in dilute aqueous sodium hydroxide solution. The basic solution was filtered with suction and the brown solid was reprecipitated from the filtrate by acidification of the filtrate with hydrochloric acid. Because the odor of

hydrogen sulfide was detected during acidification, the solid was again dissolved in dilute aqueous sodium hydroxide, and the basic solution was heated on a steam bath for 30 minutes. The solution was allowed to cool to room temperature and the brown solid was precipitated from it as before by acidification to Congo Red test paper with hydrochloric acid. The solid was isolated by suction filtration, washed with water, and allowed to dry in air to give 0.35 g. (59%) of IX. An analytical sample of IX was prepared by dissolving the crude material in dilute aqueous sodium hydroxide, filtering, acidifying the filtrate with hydrochloric acid, isolating precipitated IX by filtration, and finally washing it with water. This procedure was repeated twice to give IX as a brown powder which shrinks and blackens at 210°, then gradually decomposes as the temperature was raised. No definite melting point was observed.

Because of the insolubility of IX in water, methanol, and 95% ethanol, it was not possible to record its ultraviolet spectrum in these solvents. However, a spectrum of the disodium salt of IX in dilute aqueous sodium hydroxide was easily obtained and is as follows; U. V. λ max 217 (ϵ, 14,900), 276, shoulder (ϵ, 12,220), 298 mμ (ϵ, 16,080); infrared spectrum of IX, cm^{-1}, 3650-3050 broad band (s), 3000-2900 broad (m), 1625 (m), 1570 (m), 1530 (m), 1495 (s), 1425 (w), 1380 (w), 1315 (w), 1280 (m), 1256 (s), 1190 (w), 1120 (w), 1085 (m), 1035-1010 broad (w), 915-890 broad (w), 845 (w), 795 (w), 750-710 broad (w), 605 (m).

Anal. Calcd. for $C_7H_6N_4S_2 \cdot H_2O$: C, 36.82; H, 3.53; N, 24.54. Found: C, 36.80; H, 3.57; N, 24.49.

Acknowledgement.

This investigation was supported by Contract No. 13-0565 and Contract No. 58-1634 from Sandia Corporation, Albuquerque, N. M. The authors are indebted to Dr. M. Taylor Abegg and Mr. William J. Meikle for their interest, advice and helpful suggestions during the course of this work. Thanks are due to Mrs. Ruby Ju and to Mrs. Shigeko Nakagome for the analytical data reported.

This work was performed under the auspices of the United States Atomic Energy Commission. Reproduction in whole or in part is permitted for any purpose of the United States Government.

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(13) Structure of IX is probably the dithione form. The infrared band at 2550-2600 cm^{-1} attributable to -SH stretching (J. R. Dyer "Applications of Absorption Spectroscopy of Organic Compounds," Prentice Hall Inc., N. J., 1965, p. 38) is absent while a band at 1570 cm^{-1} indicative of C=S stretching as part of a -N-C=S system (*J. Chem. Soc.*, B, 14 (1967); R. M. Silverstein and G. C. Bassler "Spectrometric Identification of Organic Compounds," John Wiley and Sons, Inc., N. Y., 2nd Ed. (1967) p.100) is present.

Received July 28, 1967 Albuquerque, N. M. 87106