The Synthesis of Pyridazino[4,5-*d*]pyridazines, Pyrazino[2,3-*d*]pyridazines and a Pyrimido[4,5-*d*]pyridazine.

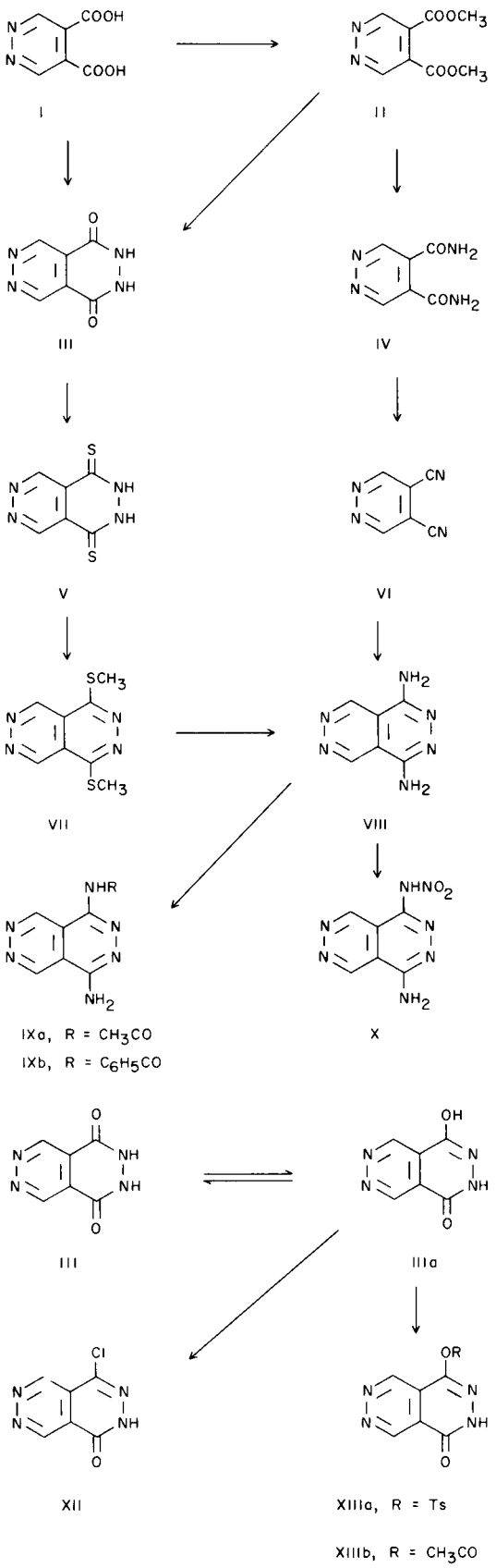
Lorraine DiStefano (1) and Raymond N. Castle (2)

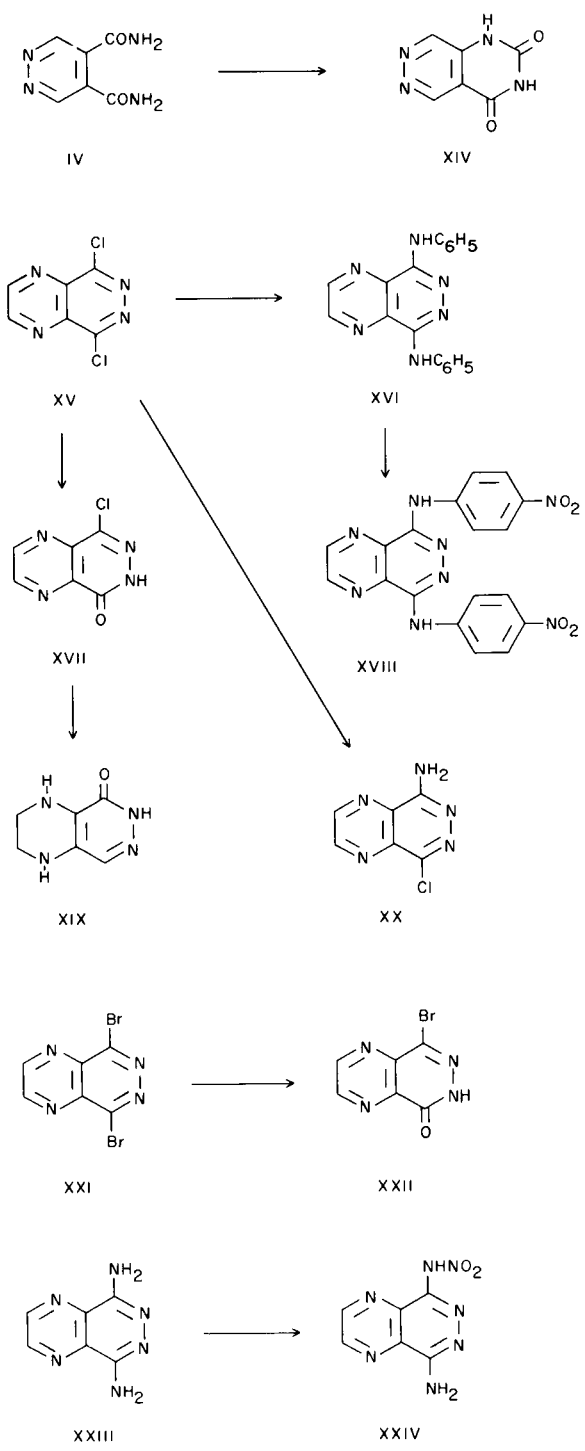
Department of Chemistry, University of New Mexico

The synthetic chemistry of the relatively unknown pyridazino[4,5-*d*]pyridazine ring system has been extended. 1,4-Diaminopyridazino[4,5-*d*]pyridazine (VIII) has been prepared by two routes, the most interesting of these being the one-step conversion of 4,5-dicyanopyridazine into VIII with hydrazine. Upon nitration VIII gave only the mononitramine (X). Attempts to prepare 1,4-dichloropyridazino[4,5-*d*]pyridazine gave only 4-chloro-2*H*-pyridazino[4,5-*d*]pyridazin-1-one (XII). Pyrimido[4,5-*d*]pyridazine-1,3-dione (XIV) was prepared from pyridazine-4,5-dicarboxamide (IV). The hydrolysis of 5,8-dichloropyrazino[2,3-*d*]pyridazine (XV) gave 5-chloropyrazino[2,3-*d*]pyridazin-8-one (XVII) and likewise the ammonolysis of XV gave 5-amino-8-chloropyrazino[2,3-*d*]pyridazine (XX). As expected the hydrolysis of 5,8-dibromopyrazino[2,3-*d*]pyridazine (XXI) gave 5-bromopyrazino[2,3-*d*]pyridazin-8-one (XXII). Attempted catalytic dechlorination of 5-chloropyrazino[2,3-*d*]pyridazin-8-one (XVII) gave 1,2,3,4-tetrahydropyrazino[2,3-*d*]pyridazin-5-one (XIX).

The known compounds in the pyridazino[4,5-*d*]-pyridazine ring system are included in four references (3,4,5,6). This research extends the preparative methods and reactions in this ring system.

Pyridazine-4,5-dicarboxylic acid (I) (7) was esterified with methanol to give dimethyl pyridazine-4,5-dicarboxylate (II). The diester (II) was heated with two moles of hydrazine in methanol solution (4) and the precipitate was heated with dilute hydrochloric acid. Pyridazino-[4,5-*d*]pyridazine-1,4-dione (III) was obtained in 86% yield. Compound III was also obtained from I directly by heating the acid (I) with 8% aqueous hydrazine in triethylene glycol (Fieser's method) (8) in 58% yield (9). The phosphorus pentasulfide thiation of III in pyridine solution gave pyridazino[4,5-*d*]pyridazine-1,4-dithione (V) in 65% yield (9). The reaction of V with two moles of methyl iodide in alkaline solution gave 1,4-bismethylthiopyridazino[4,5-*d*]pyridazine (VII) in 35% yield (10). The pressure amination of VII gave 1,4-diaminopyridazino-[4,5-*d*]pyridazine (VIII) in 71% yield. Compound VIII was also prepared in three steps from the diester (II) as described below. Dimethyl pyridazine-4,5-dicarboxylate (II) was allowed to stand with methanolic ammonia at room temperature for two days. Pyridazine-4,5-dicarboxamide (IV) (11), was obtained in 90% yield. 4,5-Dicyanopyridazine (VI) was obtained from the diamide (IV) in 60% yield by dehydration with phosphorus oxychloride. The reaction of 4,5-dicyanopyridazine (VI) with hydrazine in ethanol gave 1,4-diaminopyridazino[4,5-*d*]pyridazine (VIII) in 53% yield. Compound VIII was characterized by the preparation of the acetyl (IXa) and the benzoyl (IXb) derivatives. In each instance only a monosubstituted product was obtained. Compound VIII was nitrated under three sets of conditions (see experimental). The product was always 4-amino-1-nitraminopyridazino[4,5-*d*]pyridazine (X) in yields ranging from 50% to 66%. Attempts to rearrange the nitro group of X into the other pyridazine ring to give 1,4-diamino-5-nitropyridazino[4,5-*d*]pyridazine (XI) were unsuccessful. Attempts to prepare 1,4-dichloropyridazino[4,5-*d*]-pyridazine by the reaction of pyridazino[4,5-*d*]pyridazine-1,4-dione (III) or its tautomer IIIa by various chlorinating procedures were unsuccessful. However, when III was allowed to react with phosphorus pentachloride-phosphorus oxychloride mixtures or with phosphorus oxychloride in the presence of pyridine, 1-chloropyridazino[4,5-*d*]pyridazin-4-one (XII) was obtained in 17% yield. The reaction of III-IIIa with *p*-toluene sulfonyl chloride and acetic anhydride gave 1-(*p*-toluenesulfonyloxypyridazino[4,5-*d*]pyridazin-4-one (XIIIa) and 1-acetoxypyridazino[4,5-*d*]pyridazin-4-one (XIIIb), respectively. The ester carbonyl absorption at 1775 cm^{-1} clearly establishes the structure of XIIIb as shown in the flow sheet, however, while we prefer the





structure of XIIIa as shown (12), from the data in hand we cannot exclude the *N*-*p*-toluene-sulfonyl derivative.

The availability of pyridazine-4,5-dicarboxamide (IV) prompted the reaction of IV with potassium hypobromite. The product, pyrimido[4,5-*d*]pyridazine-2,4-dione (XIV) was obtained in 87% yield.

Prior to the publication of an article on pyrazino[2,3-*d*]-pyridazines from this laboratory by Patel and Castle (13), only two compounds were known (14, 15, 16). In this communication we describe an extension of the synthetic chemistry of this ring system. 5,8-Dichloropyrazino-[2,3-*d*]pyridazine (XV) (13) gave 5,8-bisanilinopyrazino-[2,3-*d*]pyridazine (XVI) as previously described (13). Nitration of XVI gave 5,8 bis(4-nitroanilino)pyrazino-[2,3-*d*]pyridazine (XVIII) in yields ranging from 21% to 75% depending upon nitration conditions, and the structure was assigned from the infrared spectrum (see experimental). We have found that amination of XV under pressure led only to monosubstitution similar to the experience of Patel and Castle (13) with strong amines. The product was 5-amino-8-chloropyrazino[2,3-*d*]pyridazine (XX) in 64% yield. Likewise, hydrolysis of XV with 2% sodium hydroxide solution gave only 5-chloropyrazino[2,3-*d*]-pyridazin-8-one (XVII) in 82% yield. Furthermore, 5,8-dibromopyrazino[2,3-*d*]pyridazine (XXI) gave 5-bromopyrazino[2,3-*d*]pyridazin-8-one (XXII) in 88% yield upon mild alkaline hydrolysis. Attempts to catalytically dechlorinate XVII led to 1,2,3,4-tetrahydro-pyrazino[2,3-*d*]pyridazin-5-one (XIX). The experience with this reaction is parallel to the experience of Nitta, *et al.*, (17) when they attempted to catalytically dechlorinate 5-chloropyrido[2,3-*d*]pyridazin-8-one. The nitration of 5,8-diaminopyrazino[2,3-*d*]pyridazine (XXIII) gave 5-nitramino-8-aminopyrazino[2,3-*d*]pyridazine (XXIV) in 40% yield.

EXPERIMENTAL (18)

Pyridazine-4,5-dicarboxylic Acid (I).

This compound was prepared by the method of Gabriel and Sonn (7).

Dimethyl Pyridazine-4,5-dicarboxylate (II).

Pyridazine-4,5-dicarboxylic acid (1 g., 0.006 mole) in 20 ml. of dry methanol was saturated with dry hydrogen chloride gas at room temperature for 20 minutes. The solution was allowed to stand overnight, and the excess methanol was removed by rotatory evaporation to give a thick yellow liquid. Water (15 ml.) was added and the solution was neutralized with solid sodium carbonate to a *p*H ~ 8 while cooling in an ice bath. The solution was extracted with ether, dried over magnesium sulfate and evaporated to give 0.75 g. (64%) of a yellow liquid of dimethyl pyridazine-4,5-dicarboxylate. The ester which is usually a liquid at room temperature can be solidified if evacuated for two hours. White flakes were obtained; infrared cm^{-1}, 3400(s), 2960(m), 1725(m), 1625(s), 1455(w), 1265(s), 1090(m), 1020(s), 800(s), 605(s), 460(m); NMR spectrum (deuteriochloroform), 2.35 δ (C_4 and C_5 $COOCH_3$ singlet), 7.85 δ (C_3-H and C_6-H singlet).

Anal. Calcd. for $C_8H_8N_2O_4$: C, 48.98; H, 4.11. Found: C, 49.31; H, 4.27.

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

Method A.

To a solution of 3.92 g. (0.02 mole) of dimethyl pyridazine-4,5-dicarboxylate in 50 ml. of methanol was added with stirring 3 g. (0.06 mole) of hydrazine hydrate. The mixture was refluxed with stirring for one hour, cooled, the dark yellow hydrazine salt was separated by filtration and the solid was washed with methanol. This substance was suspended in 100 ml. of water, heated to 85° with stirring and acidified with concentrated hydrochloric acid to *p*H ~ 3. After stirring for 20 minutes at 85-90°, the mixture was cooled and the product was separated by filtration. The product was washed with water and dried to give 2.80 g. (86%) of pyridazino[4,5-*d*]pyridazine-1,4-dione. The product was recrystallized from water to give a yellow precipitate, m.p. 300° dec.; infrared cm^{-1}, 3175(s), 3075(m), 2875(m), 2130(w), 1760(w), 1680(s), 1580(s), 1460(s), 1390(w), 1355(m), 1340(m), 1285(m), 1205(s), 1134(w), 1085(w), 965(s), 945(m), 843(m), 790(s), 748(w), 705(m), 672(w), 620(s), 588(s), 575(m), 488(m), 472(w); NMR spectrum (DMSO), 9.70 δ (C_5-H and C_8-H singlet).

Anal. Calcd. for $C_6H_4N_4O_2$: C, 43.90; H, 2.46; N, 34.14. Found: C, 44.21; H, 2.90; N, 34.48.

Method B.

Pyridazine-4,5-dicarboxylic acid (1 g., 0.006 mole) was dissolved in 2 ml. of an 8% solution of hydrazine. To this suspension was added 3 ml. of triethylene glycol and the mixture was heated to boiling. The excess water was removed by inserting a tube connected to a water aspirator into the upper part of the neck of the flask. Water was removed until the contents of the flask reached 130°. At this time the temperature rose rapidly to 200°. The solution was allowed to reflux for 2 minutes. The solution was cooled to 100° and 15 ml. of hot water was added. A yellow precipitate was collected and recrystallized from water to give 0.5 g. (51%) of pyridazino[4,5-*d*]pyridazine-1,4-dione, m.p. 300° dec. The infrared spectrum of this sample was identical to the product prepared by method A above.

Pyridazino[4,5-*d*]pyridazine-1,4-dithione (V).

Pyridazino[4,5-*d*]pyridazine-1,4-dione (0.3 g., 0.002 mole) was heated with 20 ml. of dry pyridine while stirring. To the boiling solution was added slowly, portion-wise, 0.888 g. (0.004 mole) of phosphorus pentasulfide. The solution was heated under reflux for one hour. The solution was cooled and the excess pyridine was removed by distillation under reduced pressure. The residue was cooled and ice was added to replace the distilled pyridine. The solution was heated on a steam bath for 2 hours, filtered and acidified to congo red with hydrochloric acid. A brownish-black precipitate (0.27 g., 65%) was filtered and dissolved in a 10% sodium hydroxide solution. Reprecipitation with concentrated hydrochloric acid gave a black residue which was purified by two more acid-base precipitations and refluxed in 95% ethanol for one-half hour to give pyridazino[4,5-*d*]pyridazine-1,4-dithione, m.p. > 300°; U.V. λ max (0.1 *N* sodium hydroxide), 257 (ϵ, 12,110), 310 (ϵ, 3,150), 412 mμ (ϵ, 6,100); infrared cm^{-1}, 2925(w), 1630(w), 1525(m), 1475(m), 1425(m), 1287(w), 1275(w), 1255(s), 1205(m), 1165(w), 1060(w), 1035(w), 945(m), 815(w), 750(s), 730(m), 680(s), 630(s), 610(m), 535(w), 465(w).

Anal. Calcd. for $C_6H_4N_4S_2 \cdot 0.5H_2O$ C, 35.11; H, 2.45; N, 27.29. Found: C, 35.14; H, 2.93; N, 27.60.

1,4-bis(Methylthio)pyridazino[4,5-*d*]pyridazine (VII).

Methyl iodide (12.5 g., 0.087 mole) in 20 ml. of ethanol was added portionwise to 2 g. (0.010 mole) of pyridazino[4,5-*d*]-pyridazine-1,4-dithione (V) dissolved in a mixture of 8 ml. of 10% sodium hydroxide solution and 15 ml. of 28% ammonium hydroxide. A precipitate began to separate during the addition. Stirring was continued for 24 hours at room temperature. The

solid was collected, washed with 50 ml. of ethanol, dried overnight, and recrystallized from water to give yellow flakes, yield 0.65 g. (32%), m.p. 195°; U.V. λ max (95% ethanol); 203, 212 (sh) (ε, 13,540), 234 (sh) (ε, 8,817), 259(sh) (ε, 3,860), 282 (ε, 2,930), 347 mμ (ε, 7,506); infrared cm^{-1}; 3425(w), 3050(w), 2940(w), 1475(s), 1420(m), 1330(m), 1304(m), 1290(s), 1280(s), 1040(m), 960(w), 925(m), 910(m), 822(w), 731(m), 707(w), 605(m), 594(m), 540(w), 525(w), 450(m).

Anal. Calcd. for $C_8H_8N_4S_2$: C, 42.84; H, 3.51; N, 24.98. Found: C, 43.25; H, 3.59; N, 24.95.

1,4-Diaminopyridazino[4,5-*d*]pyridazine (VIII).

Method A.

A mixture containing 0.7 g. (0.00312 mole) of 1,4-bis-(methylthio)pyridazino[4,5-*d*]pyridazine in 100 ml. of absolute ethanol saturated with ammonia at 0-5° was heated in a stainless steel reaction vessel in a rocking autoclave at 195-205° for 26 hours. The solution was heated on a steam bath and filtered while hot. The filtrate was evaporated to dryness to yield 0.35 g. (71%) of a yellow residue. The residue was recrystallized from methanol to give yellow crystals of 1,4-diaminopyridazino[4,5-*d*]-pyridazine, m.p. > 300°; U.V. λ max (95% ethanol); 211 (ε, 24,420), 217 (sh), (ε, 12,030), 315 mμ (ε, 3,915); infrared cm^{-1}; 3300(s), 3075(s), 1650(s), 1625(s), 1575(w), 1550(m), 1460(w), 1425(m), 1390(m), 1283(w), 1268(s), 1055(s), 935(m), 925(s), 790(w), 770(m), 680(w), 590(w), 575(m), 510(m), 425(m).

Anal. Calcd. for $C_6H_6N_6$: C, 44.44; H, 3.73; N, 51.83. Found: C, 44.27; H, 4.07; N, 51.66.

Method B.

A solution containing 4,5-dicyanopyridazine (0.3 g., 0.0024 mole) and 10 ml. of absolute methanol was stirred magnetically at room temperature. To the methanolic solution was added dropwise 0.6 ml. of 95% hydrazine. The reaction mixture was stirred overnight at room temperature and evaporated to dryness the following day. The dry, brown residue was powdered and sublimed under a pressure of 0.05 mm. in an oil bath at 130-160°. The product was 0.2 g. (53%) of yellow crystals of 1,4-diaminopyridazino[4,5-*d*]-pyridazine, m.p. > 300°. The infrared spectrum of this sample was identical with that of the sample prepared by method A.

Pyridazine-4,5-dicarboxamide (IV).

Dimethyl pyridazine-4,5-dicarboxylate (0.75 g., 0.004 mole) was added to 25 ml. of methanolic ammonia prepared by saturating anhydrous methanol with ammonia for one-half hour. The flask was stoppered and allowed to stand for 2 days. White crystals, 1 g. (> 90%), m.p. 249-252° (Lit. 246-248°), (11) were obtained.

4,5-Dicyanopyridazine (VI).

Pyridazine-4,5-dicarboxamide (2.5 g., 0.15 mole) was suspended in 25 ml. of phosphorus oxychloride and the mixture was stirred at room temperature for 4 hours and then refluxed for 3 hours. The excess of phosphorus oxychloride was removed under reduced pressure and the residue was dried over sodium hydroxide in an evacuated desiccator. The residue was suspended in 75 ml. of saturated sodium carbonate solution at 5° and the aqueous alkaline solution was extracted with 5 x 50 ml. of ether. The combined ether extracts were washed with 15 ml. of a saturated aqueous sodium chloride solution. The ethereal solution was dried over anhydrous sodium sulfate. The sodium sulfate was removed by filtration and the ether evaporated to give 1.1 g. (60%) of 4,5-dicyanopyridazine, light yellow needles, m.p. 136-137° from ethanol; U.V. λ max (95% ethanol); 206 (ε, 7,046), 228 (ε, 7,349), 279 mμ (ε, 2,222); infrared cm^{-1}; 3100(w), 3075(s), 2230(w), 1550(w), 1535(m), 1440(w), 1425(m), 1313(m), 1290(s), 1247(w), 1176(w), 1161(w), 1133(m), 1003(s), 928(s), 878(w), 842(m), 758(s), 605(w); NMR spectrum (deuteriochloroform), 9.63 δ (C_3-H and C_6-H singlet).

Anal. Calcd. for $C_6H_2N_4$: C, 55.37; H, 1.55; N, 43.07. Found: C, 55.76; H, 1.60; N, 43.51.

1-Amino-4-acetylaminopyridazino[4,5-*d*]pyridazine (IXa).

A mixture of 0.2 g. (0.0012 mole) of 1,4-diaminopyridazino-[4,5-*d*]pyridazine and 1 ml. of acetic anhydride was heated under reflux for one hour. After heating ten minutes, the compound dissolved and then a precipitate appeared. After cooling, cold water was poured into the solution and 0.2 g. of a light yellow precipitate was removed by filtration. The precipitate was dissolved in water (Norite) and 0.12 g. (50%) of light yellow crystals of 1-amino-4-acetylaminopyridazino[4,5-*d*]pyridazine, m.p. > 270°, was obtained; U.V. λ max (distilled water); 219 (ε, 21,800), 267 mμ (ε, 4,223); infrared cm^{-1}, 3200(w), 3000(m), 1670(s), 1585(s), 1550(s), 1490(m), 1445(m), 1410(m), 1375(m), 1340(w), 1305(s), 1280(w), 1245(m), 1150(w), 1120(m), 1035(w), 1020(m), 980(m), 955(s), 818(m), 750(m), 655(w), 602(m), 578(w), 565(m), 495(w), 428(s); NMR spectrum (deuterium oxide, hydrochloric acid); 2.36 δ (C-CH_3 singlet), 9.66 δ (C_8-H and C_5-H).

Anal. Calcd. for $C_8H_8N_6O$: C, 47.06; H, 3.94; N, 41.16. Found: C, 47.51; H, 4.17; N, 40.88.

1-Amino-4-benzoylaminopyridazino[4,5-*d*]pyridazine (IXb).

1,4-Diaminopyridazino[4,5-*d*]pyridazine (0.2 g., 0.0012 mole) was added to a solution of 0.33 g. of benzoyl chloride in 20 ml. of dry pyridine. Benzene (20 ml.) was added and the solution was heated to reflux in an oil bath with stirring for 2 hours. The resulting mixture was poured into cold water and the benzene layer was separated. After drying the benzene solution over magnesium sulfate and filtering, the excess benzene was removed by evaporation on a rotatory evaporator. Some toluene was added to the resulting oil and hexane was added dropwise until a yellow solid (0.12 g., 40%), m.p. 229-230° precipitated. The precipitate was recrystallized from ethanol and benzene to give white flakes of 1-amino-4-benzoylaminopyridazino[4,5-*d*]pyridazine, m.p. 237-240°; U.V. λ max (95% ethanol); 225 (ε, 18,260), 274 mμ (ε, 6,071); infrared cm^{-1}, 3425(m), 3160(w), 1780(w), 1700(s), 1600(s), 1555(m), 1530(s), 1450(m), 1415(m), 1380(s), 1330(m), 1260(s), 1205(m), 1125(m), 1065(m), 1030(w), 970(m), 897(s), 820(w), 787(w), 705(s), 675(m), 615(w).

Anal. Calcd. for $C_{13}H_{10}N_6O$: C, 58.64; H, 3.78; N, 31.56. Found: C, 58.82; H, 4.03; N, 31.33.

1-Nitramino-4-aminopyridazino[4,5-*d*]pyridazine (X).

Method A.

To a cold solution of 2 ml. of concentrated sulfuric acid at 0° was added 0.5 g. (0.0031 mole) of 1,4-diaminopyridazino[4,5-*d*]-pyridazine. The temperature of the mixture was allowed to rise to room temperature in order to allow all the solid material to dissolve and then cooled again to 0°. A previously prepared mixture of concentrated nitric acid-concentrated sulfuric acid (1:1) was chilled to 5°. One ml. of the acid solution was added dropwise to the stirred mixture. The solution was stirred for 20 minutes at 5°. Ice was added and a yellow precipitate (0.41 g., 66%) was collected and washed with water. The precipitate was recrystallized from water to give 1-nitramino-4-aminopyridazino[4,5-*d*]pyridazine, m.p. 249-250°, (decomposed audibly with the evolution of gas); U.V. λ max (distilled water); 226 (ε, 17,520), 310 mμ (ε, 7,270); infrared cm^{-1}, 3007(m), 1610(s), 1530(s), 1498(m), 1425(s), 1320(s), 1220(s), 1150(m), 1075(m), 1025(w), 1000(w), 960(m), 920(m), 790(m), 765(m), 742(w), 675(w), 645(m), 590(w), 490(m), 430(m).

Anal. Calcd. for $C_6H_5N_7O_2$: C, 34.78; H, 2.41. Found: C, 34.45; H, 2.61.

Method B.

To 1,4-diaminopyridazino[4,5-*d*]pyridazine (0.2 g., 0.0012 mole), cooled to 0° in an ice bath, was added 0.5 ml. of 90% nitric acid, dropwise while stirring. The solution was stirred for 20 minutes at 10°. Cracked ice was added and a yellow precipitate (0.2 g.) was filtered and washed with water. The dried precipitate was recrystallized from water giving 0.15 g. (60%) of yellow compound, m.p. 249-250° (decomposed audibly with the evolution of gas). The compound was identified by comparison of the infrared and ultraviolet spectra of the previously prepared (method A) 1-nitramino-4-aminopyridazino[4,5-*d*]pyridazine.

Method C.

A slightly lower yield (50%) of the nitramine was obtained by using concentrated nitric acid in place of 90% nitric acid.

Attempted Rearrangement of 1-Amino-4-nitraminopyridazino-[4,5-*d*]pyridazine (X).

To a cold solution of 2 ml. of concentrated sulfuric acid at 0° was added 2 g. (0.001 mole) of 1-amino-4-nitraminopyridazino-[4,5-*d*]pyridazine (X). The mixture was allowed to rise to room temperature and then heated on a water bath at 45° for one-half hour. The solution was poured over cracked ice and allowed to stand overnight in the refrigerator. A solid did not separate upon standing or upon neutralization with solid sodium carbonate. Attempts to isolate a product were not successful.

1-Chloropyridazino[4,5-*d*]pyridazin-4-one (XII).

Method A.

Pyridazino[4,5-*d*]pyridazine-1,4-dione (III) (5 g., 0.030 mole) was heated under reflux with 5 g. of phosphorus pentachloride and 70 ml. of phosphorus oxychloride for 2 days. The excess phosphorus oxychloride was removed by distillation and the residue poured over ice, neutralized with sodium hydroxide and extracted with ether in a continuous liquid-liquid extractor for 2 days. Evaporation of ether gave a dark yellow residue (0.5 g.), m.p. 280°, which was recrystallized from ethanol to give light yellow crystals of 4-chloropyridazino[4,5-*d*]pyridazin-4-one, m.p. 283°; U.V. λ max (distilled water); 212 (sh) (ε, 7,755), 249 (sh), (ε, 4,472), 256.5 (ε, 4,887), 296 mμ (ε, 4,612); infrared cm^{-1}; 3075(m), 3060(m), 2950(m), 2850(m), 1685(s), 1585(m), 1575(m), 1540(m), 1460(w), 1360(w), 1320(m), 1315(m), 1260(w), 1205(w), 1165(s), 1120(w), 1035(w), 1020(m), 996(m), 925(m), 810(m), 757(s), 703(m), 690(w), 683(m), 630(w), 587(s), 530(m), 495(m).

Anal. Calcd. for $C_6H_3ClN_4O$: C, 39.47; H, 1.64; N, 30.69. Found: C, 39.60; H, 1.92; N, 30.33.

Method B.

Pyridazino[4,5-*d*]pyridazine-1,4-dione (III) (5 g., 0.03 mole) was heated under reflux with 4 ml. of pyridine and 10 ml. of phosphorus oxychloride for 4 hours. The excess phosphorus oxychloride was removed by distillation and the residue was poured over ice. The dark brown precipitate was filtered, dissolved in ethanol and evaporated to a small volume. One gram (17%) of light yellow needles, m.p. 283° crystallized. Comparison of the infrared spectrum of this compound with that of XII prepared by method A above established the identity of this compound as 1-chloropyridazino[4,5-*d*]pyridazin-4-one.

When the above procedure was modified by using dimethylaniline in place of pyridine, no product could be isolated.

4-(*p*-Toluenesulfonyloxy)-2*H*-pyridazino[4,5-*d*]pyridazin-1-one (XIIIa).

A solution containing 0.2 g. (0.0012 mole) of pyridazino-[4,5-*d*]pyridazin-1,4-dione (III) in 35 ml. of dry pyridine was obtained by warming the mixture. The solution was cooled, stirred magnetically and 0.57 g. of *p*-toluenesulfonyl chloride was added. The mixture was stirred for 12 hours at room temperature and then at 55° for 2 hours under anhydrous conditions. The clear solution was added to 100 g. of crushed ice. After evaporation of some excess water, 0.28 g. (65%) of a yellow precipitate was filtered, dried and recrystallized from ethanol (Norite) to give light yellow flakes of 4-(*p*-toluenesulfonyloxy)-2*H*-pyridazino-[4,5-*d*]pyridazin-1-one, m.p. 225-226°; U.V. λ max (95% ethanol); 204, 226 (ε, 14,970), 260 mμ (sh) (ε, 4,525); infrared cm^{-1}, 3440(s), 3060(w), 2550(w), 1700(s), 1610(s), 1550(w), 1490(w), 1375(s), 1325(m), 1270(m), 1205(s), 1185(s), 1140(w), 1095(m), 1075(m), 1020(w), 975(s), 875(w), 847(w), 814(m), 748(m), 708(s), 684(m), 667(s), 615(s), 574(s), 547(s), 511(w), 490(w),

Anal. Calcd. for $C_{13}H_{10}N_4O_2S$: C, 49.04; H, 3.16; N, 17.60. Found: C, 49.16; H, 3.52; N, 17.85.

4-Acetoxy-2*H*-pyridazino[4,5-*d*]pyridazin-1-one (XIIIb).

To 10 ml. of acetic anhydride was added 1 g. (0.006 mole) of pyridazino[4,5-*d*]pyridazine-1,4-dione (III). The reaction mixture was heated under reflux for 2 hours. The mixture was cooled to room temperature and then evaporated to dryness using a rotatory evaporator. The brown residue was dried in a vacuum oven at 70°. This material was boiled in ethanol, filtered and evaporated to give 0.2 g. (20%) of a light yellow compound. The precipitate was recrystallized from ethanol to give light yellow flakes of 4-acetoxy-2*H*-pyridazino[4,5-*d*]pyridazin-1-one, m.p. 245-246°; U.V. λ max (95% ethanol); 212 (ε, 7,777), 371 (ε, 5,946), 390 mμ (ε, 4,426); infrared cm^{-1}; 3060(w), 2990(m), 1775(s), 1700(s), 1625(s), 1560(m), 1530(m), 1420(s), 1365(s), 1335(s), 1305(s), 1285(w), 1240(s), 1180(s), 1117(s), 1090(s), 1030(s), 1010(m), 923(m), 880(s), 860(s), 805(m), 778(m), 756(m), 710(s), 665(w), 620(m), 603(m), 583(w), 555(m), 536(w), 515(m).

Anal. Calcd. for $C_8H_6N_4O_3$: C, 46.61; H, 2.93; N, 27.18. Found: C, 46.87; H, 3.21; N, 27.01.

Pyrimido[4,5-*d*]pyridazine-2,4-dione (XIV).

A hypobromite solution was prepared by dissolving 3.7 g. of potassium hydroxide in 10 ml. of water and adding 24 g. of ice. To the cold solution was added slowly with stirring 2 g. of bromine. A light yellow solution was obtained and to it was added all at once 1 g. (0.006 mole) of pyridazine-4,5-dicarboxamide with stirring. Stirring was continued until solution was complete. The solution was allowed to stand overnight in the refrigerator. The mixture was then heated on a steam bath for one hour. The solution became turbid. The mixture was cooled and acidified with glacial acetic acid to *p*H ~ 4, whereupon a tan-colored precipitate was obtained. The precipitate was filtered, dried and recrystallized from water to give 0.86 g. (87%) of white pyrimido[4,5-*d*]-pyridazine-2,4-dione, m.p. > 360°; U.V. λ max 95% ethanol); 214 (ε, 24,680), 247 (ε, 8,033), 284 mμ (ε, 3,822); infrared cm^{-1};

3025(s), 2800(s), 1710(s), 1595(s), 1485(w), 1440(m), 1410(s), 1325(m), 1285(m), 1200(w), 1155(s), 1015(s), 970(m), 940(w), 920(m), 800(w), 788(w), 765(m), 755(w), 740(w), 715(s), 645(s), 590(m), 555(w), 505(s), 465(m); NMR spectrum (deuterium oxide, sodium hydroxide), 8.75 δ (C_8-H doublet), 8.93 δ (C_5-H doublet); $J_{5,8}$=1.1 cps.

Anal. Calcd. for $C_6H_4N_4O_2$: C, 43.90; H, 2.45; N, 34.07. Found: C, 43.77; H, 2.79; N, 34.12.

5-Chloropyrazino[2,3-*d*]pyridazin-8-one (XVII).

5,8-Dichloropyrazino[2,3-*d*]pyridazine (0.4 g., 0.002 mole) was heated with 10 ml. of 2% sodium hydroxide until a clear light

yellow solution was obtained. Norite was added and the solution was boiled and filtered. After cooling, the solution was made acidic with acetic acid. A slight reduction in the volume by boiling afforded 0.32 g. of yellow white needle like crystals m.p. 270-272°. Recrystallization from water (Norite) gave 0.3 g. (82%) of white needles of 5-chloropyrazino[2,3-*d*]pyridazin-8-one, m.p. 271°; U.V. λ max (distilled water); 205 (ε, 16,690), 256 (ε, 11,150), 318 mμ (ε, 3,617); infrared cm^{-1}; 3060(s), 2890(w), 2860(w), 1990(w), 1710(s), 1640(s), 1575(s), 1540(w), 1475(w), 1445(s), 1400(m), 1350(m), 1318(s), 1230(s), 1175(s), 1134(s), 1042(s), 1009(s), 895(m), 845(m), 825(m), 740(m), 655(s), 620(s), 543(m), 485(s), 430(s).

Anal. Calcd. for $C_6H_3ClN_4O$: C, 39.46; H, 1.64; N, 30.69. Found: C, 39.56; H, 1.81; N, 30.24.

1,2,3,4-Tetrahydropyrazino[2,3-*d*]pyridazin-5-one (XIX).

To a solution of 40 ml. of methanol was added 0.4 g. (0.0022 mole) of 5-chloropyrazino[2,3-*d*]pyridazin-8-one (XVII), 0.44 ml. of concentrated ammonium hydroxide and 0.44 g. of 10% palladium on charcoal. Since the 5-chloropyrazino[2,3-*d*]pyridazin-8-one did not go into the methanol solution an excess amount of sodium hydroxide was added to effect solution. The solution was hydrogenated at room temperature under atmospheric pressure for 12 hours during which time 230 ml. of hydrogen was absorbed. The solution was filtered and evaporated to dryness. The yellow solid was boiled in ethanol, filtered, evaporated and 0.1 g. (33%) of tan product was crystallized by the addition of chloroform. The product was recrystallized twice from ethanol-chloroform to give 0.05 g. of 1,2,3,4-tetrahydropyrazino[2,3-*d*]pyridazin-5-one, m.p. 223°; U.V. λ max (95% ethanol); 210 (ε, 11,290), 236 (ε, 18,100), 286 (ε, 3,839), 337 mμ (ε, 5,835); infrared cm^{-1}; 3300(s), 3150(s), 3000(m), 2875(w), 1615(s), 1550(s), 1500(m), 1460(w), 1420(m), 1385(s), 1330(s), 1305(w), 1290(m), 1240(s), 1175(m), 1130(s), 1075(m), 1035(m), 960(w), 940(w), 884(s), 865(s), 755(m), 680(w), 555(m).

Anal. Calcd. for $C_6H_8N_4O$: C, 47.36; H, 5.29; N, 36.82. Found: C, 47.14; H, 5.37; N, 36.60.

5-Bromopyrazino[2,3-*d*]pyridazin-8-one (XXII).

5,8-Dibromopyrazino[2,3-*d*]pyridazine (0.2 g., 0.0007 mole) was heated with 10 ml. of 2% sodium hydroxide until a clear light yellow solution was obtained. Norite was added and the solution was boiled and filtered. After cooling, the solution was made acidic with glacial acetic acid. A slight reduction in the volume by boiling, afforded 0.16 g. of yellow-white needlelike crystals, m.p. 268-270°. Recrystallization from water (Norite) gave 0.14 g. (88%) of white needles of 5-bromopyrazino[2,3-*d*]-pyridazin-8-one, m.p. 270°; U.V. λ max (distilled water); 204 (ε, 17,900), 258 (ε, 13,360), 320 mμ (ε, 4,610); infrared cm^{-1}; 3000(s), 1980(w), 1710(s), 1640(s), 1560(s), 1460(w), 1425(s), 1414(m), 1350(s), 1310(s), 1262(w), 1225(s), 1165(m), 1125(s), 1040(s), 990(s), 890(m), 840(s), 820(m), 728(s), 640(s), 610(s), 535(m), 525(w), 485(s), 430(s).

Anal. Calcd. for $C_6H_3BrN_4O$: C, 31.74; H, 1.32; N, 24.68. Found: C, 31.88; H, 1.45; N, 24.20.

5-Nitramino-8-aminopyrazino[2,3-*d*]pyridazine (XXIV).

5,8-Diaminopyrazino[2,3-*d*]pyridazine (0.2 g., 0.0012 mole) was cooled in an ice bath to 0°. With a pipette, enough 90% nitric acid was dropped slowly onto the compound, while stirring, to effect solution. The mixture was stirred for 20 minutes at 10° and then cracked ice was added. A yellow precipitate (0.2 g.) was filtered and washed with water. The dried precipitate was recrystallized from water to give 0.1 g. (40%) of gold crystals of 5-nitramino-8-aminopyrazino[2,3-*d*]pyridazine, m.p. >300°; U.V. λ max (distilled water); 209 (ε, 18,350), 262 mμ (ε, 11,640); infrared cm^{-1}; 3450(m), 3225(m), 1625(s), 1575(s), 1550(m), 1460(s), 1425(s), 1360(m), 1330(m), 1275(m), 1160(s), 1130(w), 1040(m), 880(s), 820(w), 775(m), 755(m), 720(w), 645(m), 560(w), 495(w), 430(m).

Anal. Calcd. for $C_6H_5N_7O_2$: C, 34.78; H, 2.41; N, 47.34. Found: C, 34.57; H, 2.71; N, 47.02.

5-Amino-8-Chloropyrazino[2,3-*d*]pyridazine (XX).

5,8-Dichloropyrazino[2,3-*d*]pyridazine (0.2 g., 0.0012 mole) was heated with 5 ml. of concentrated ammonium hydroxide in a pressure vessel at 120° for 24 hours. A light brown solid was filtered, washed with water and dried. The brown solid was sublimed at 0.01 mm. pressure in an oil bath at a temperature of 140-170° to give 0.09 g. of yellow crystals. The unsublimed material was dissolved in water, filtered and 0.05 g. of additional product crystallized. The total yield was 0.14 g. (64%) of 5-amino-8-chloropyrazino[2,3-*d*]pyridazine, m.p. 263-265°; U.V. λ max (95% ethanol); 211 (ε, 17,250), 222 (sh), (ε, 12,500), 265 mμ (ε, 14,300); infrared cm^{-1}; 3400(s), 3340(m), 2925(m), 2850(w), 1550(s), 1475(m), 1375(s), 1325(s), 1310(w), 1285(s), 1185(m), 1145(m), 1065(m), 1000(s), 865(m), 750(m), 615(w), 535(w), 487(w); NMR spectrum (deuterium oxide, hydrochloric acid); 9.40 δ (C_2-H and C_3-H singlet).

Anal. Calcd. for $C_6H_4ClN_5$: C, 39.69; H, 2.20. Found: C, 39.91; H, 2.45.

5,8-Dianilinopyrazino[2,3-*d*]pyridazine (XVI).

A mixture of 5,8-dichloropyrazino[2,3-*d*]pyridazine (0.6 g., 0.003 mole), aniline (0.49 g.) and 15 ml. of ethanol was heated under reflux for 4 hours. The solution was allowed to come to room temperature and made alkaline with ammonium hydroxide. A red solid was filtered and recrystallized from ethanol to give 0.65 g. (72%) of red needles of 5,8-dianilinopyrazino[2,3-*d*]-pyridazine, m.p. 242-243° (Lit. 242-243°, (13)).

5,8-bis(4-Nitroanilino)pyrazino[2,3-*d*]pyridazine (XVIII).

Method A.

5,8-Dianilinopyrazino[2,3-*d*]pyridazine (0.15 g., 0.00048 mole) was cooled to 0°. Nitric acid (0.5 ml., 90%) was added dropwise, with stirring to the compound until a dark brown mixture was obtained. This mixture was stirred for one-half hour at 2°, and ice was added. An orange-brown precipitate was filtered, washed with water and dried. The precipitate was dissolved in acetone and precipitated with water to give 0.12 g. (75%) of 5,8-bis(4-nitroanilino)pyrazino[2,3-*d*]pyridazine, m.p. > 300°; U.V. λ max (95% ethanol); 208, 248, 362, 446 mμ (saturated solution); infrared cm^{-1}; 3350(m), 3100(w), 1610(s), 1565(w), 1525(s), 1500(s), 1450(w), 1425(m), 1330(s), 1315(m), 1270(s), 1245(s), 1185(m), 1150(m), 1118(s), 1045(w), 1020(w), 910(w), 856(m), 850(m), 820(m), 750(s), 700(w), 690(m), 665(w), 495(w), 435(m).

Anal. Calcd. for $C_{18}H_{12}N_8O_4$: C, 53.47; H, 2.98; N, 27.71. Found: C, 53.01; H, 3.22; N, 27.45.

Method B.

A slightly lower yield (52%) of the dinitroanilino compound was obtained using the same procedure as in method A, except that concentrated nitric acid was used instead of 90% nitric acid. Infrared spectra and the melting points were identical with those of the compound synthesized by method A.

Method C.

5,8-Dianilinopyrazino[2,3-*d*]pyridazine (0.2 g., 0.0006 mole) was added slowly to a mixture containing 2 ml. of 100% nitric acid and 2 ml. of concentrated sulfuric acid at 0°. The mixture was stirred for 5 minutes and the temperature was allowed to rise to 50°. The solution was stirred 3 hours at 50°, cooled and poured into ice. A greenish-yellow precipitate separated and was removed by filtration. The precipitate was boiled in water. filtered and evaporated to give a yellow residue. The residue was dissolved in acetone, filtered, evaporated and recrystallized from water to give 0.05 g. (21%) of a yellow compound, m.p. $>300°$. The infrared spectrum and melting point were identical with those described above.

Acknowledgment.

This investigation was fupported by Contract No. 13-0565 and Contract No. 58-1634 from Sandia Corporation, Albuquerque, New Mexico. 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 Miss Dianne Dottavio for the preparation of starting materials 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.

REFERENCES

(1) Present address: Research Laboratories, Parke, Davis and Company, Ann Arbor, Michigan 48106.

(2) Inquiries concerning this paper should be addressed to Professor Raymond N. Castle.

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

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

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

(6) L. C. Dorman, *J. Heterocyclic Chem.*, 4, 491 (1967).

(7) S. Gabriel and A. Sonn. *Ber.*, 40, 4857 (1907).

(8) L. F. Fieser, "Experiments in Organic Chemistry," D. C. Heath and Co., Boston, Mass, 1955, p. 109.

(9) L. C. Dorman, see reference 6 above obtained III in 87% yield by exactly the same method.

(10) L. C. Dorman, see reference 6 above, obtained VII in 38% yield.

(11) I. Satoda, N. Yoshida and K. Mori, *Yakugaku Kenkyu*, 28, 609 (1956).

(12) N. Kakimoto, *Nippon Kagaku Zasshi*, 79, 1403 (1958).

(13) N. Patel and R. N. Castle, *J. Heterocyclic Chem.*, 3, 512 (1966).

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

(15) P. Hemmerich and S. Fallab, *Helv. Chim. Acta*, 41, 489 (1958).

(16) I. Hagedorn and H. Toenjas, *Pharmazie*, 12, 567 (1957).

(17) Y. Nitta, I. Matsuura and F. Yoneda, *Chem. Pharm. Bull.*, 13, 586 (1965).

(18) All melting points were determined in a Thomas-Hoover capillary melting point apparatus or in a copper block and are uncorrected. The infrared spectra were determined with a Perkin-Elmer 337 Spectrophotometer in potassium bromide discs. The ultraviolet spectra were taken in the solvent indicated with a Bausch and Lomb Spectronic 505 Spectrophotometer. The Nuclear Magnetic Resonance spectra were taken in the solvent indicated with a Varian A 60 A Spectrophotometer. The NMR spectra were compared with TMS as an internal standard except when deuterium oxide was the solvent; then TMS was used as an external standard.

Received December 18, 1967 Albuquerque, N. M. 87106