The Synthesis of Pyrimido[4,5-*c*]pyridazines and Pyrimido[5,4-*c*]pyridazines.

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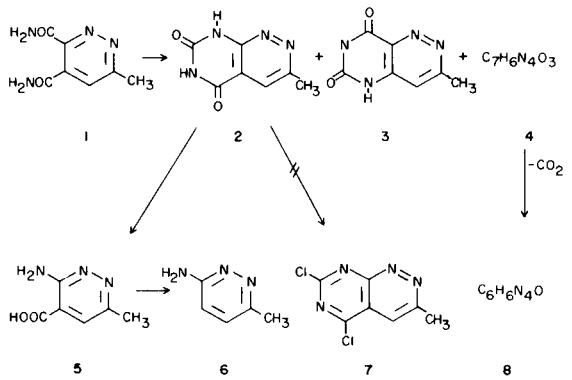
The Hofmann reaction on 6-methylpyridazine-3,4-dicarboxamide (**1**) gave a mixture of 3-methylpyrimido[4,5-*c*]pyridazine-5,7-dione (**2**), 3-methylpyrimido[5,4-*c*]pyridazine-6,8-dione (**3**) and an acid (**4**) of unknown structure. The Hofmann reaction on pyridazine-3,4-dicarboxamide (**9**) gave a mixture of pyrimido[4,5-*c*]pyridazine-5,7-dione (**10**) and an acid (**11**) of unknown structure. The reaction of 3-amino-6-methylpyridazine-4-carboxamide (**18**) with ethyl orthoformate gave 3-methylpyrimido[4,5-*c*]pyridazin-5-one (**21**). 4-Aminopyridazine-3-carboxamide (**36**) upon fusion with urea gave pyrimido[5,4-*c*]pyridazine-6,8-dione (**37**) while with ethyl orthoformate **36** gave pyrimido[5,4-*c*]pyridazin-8-one (**38**). Pyrimido[5,4-*c*]-pyridazine-8-thione (**39**) was obtained by the action of phosphorus pentasulfide on **38**. 4-Amino-3-cyanopyridazine (**16**) when treated with formamide produced 8-aminopyrimido[5,4-*c*]-pyridazine (**41**). The synthesis of 4-aminopyridazine-3-carboxamide (**36**) and 4-amino-3-cyano-pyridazine (**16**), both key intermediates in the synthesis of the novel pyrimido[5,4-*c*]pyridazine ring system was accomplished by the Reissert reaction of 4-aminopyridazine-2-oxides and subsequent conversion of the nitrile to the amide.

The purpose of this investigation was the synthesis of 3-methylpyrimido[4,5-*c*]pyridazine-5,7-dione (**2**) and 3-methylpyrimido[5,4-*c*]pyridazine-6,8-dione (**3**). These two compounds comprise key intermediates for the synthesis of folic acid analogs in these two ring systems. The synthesis of 3-methylpyrimido[5,4-*c*]pyridazine-6,8-dione (**3**), pyrimido[5,4-*c*]pyridazine-6,8-dione (**37**), pyrimido[5,4-*c*]pyridazine-8-one (**38**), pyrimido[5,4-*c*]-pyridazine-8-thione (**39**) and 8-aminopyrimido[5,4-*c*]-pyridazine (**41**) has been accomplished. Members of this ring system have not been reported previously in the literature.

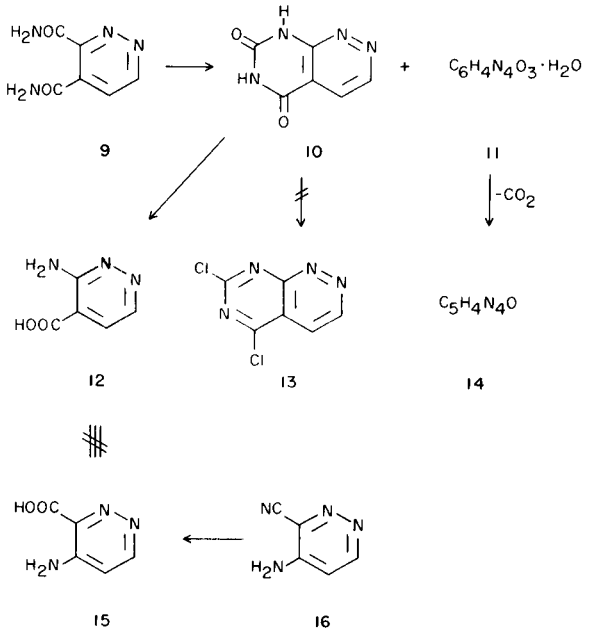
Jones (3) had carried out the Hofmann reaction on 6-methylpyridazine-4,5-dicarboxamide (**1**). He obtained a product to which he assigned the structure 3-methyl-pyrimido[4,5-*c*]pyridazine-5,7-dione (**2**) but indicated the structural assignment was tentative. We have repeated this reaction and obtained three products. The main product was that described by Jones (3). We have established that the structural assignment made by Jones was correct by the alkaline ring opening of **2**. Thus 3-amino-6-methyl-pyridazine-4-carboxylic acid (**5**) was obtained by the acid catalyzed ring opening of **2**. For structure proof, the the 3-amino-6-methylpyridazine-4-carboxylic acid (**5**) was decarboxylated into the known 3-amino-6-methylpyrida-zine (**6**) (4). Since the structure of **2** is now certain, the structure of the isomeric 3-methylpyrimido[5,4-*c*]pyrida-zine-6,8-dione (3) is established by elimination. The third product, the acid (**4**) ($C_7H_6N_4O_3$) was decarboxy-lated to the unknown compound **8**, $C_6H_6N_4O$. Attempts to chlorinate 3-methylpyrimido[4,5-*c*]pyridazine-5,7-dione (**2**) with phosphorus oxychloride or phosphorus oxychloride-phosphorus pentachloride mixtures were unsuccessful. A product with the properties expected of 5,7-dichloro-3-methylpyrimido[4,5-*c*]pyridazine (**7**) could not be isolated. These reactions are shown in the Flow Sheet I.

Flow Sheet I



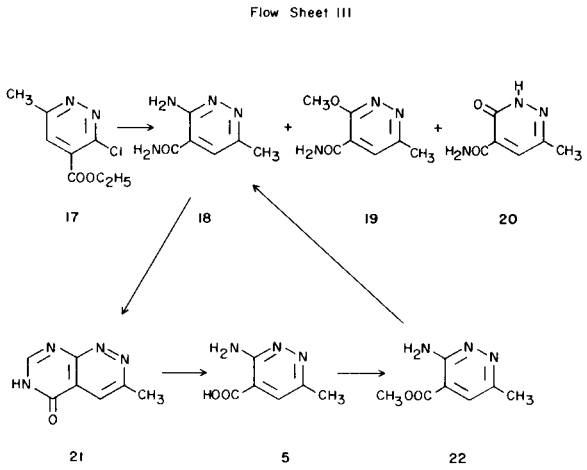
When pyridazine-3,4-dicarboxamide (**9**) (5) was subjected to the Hofmann reaction, pyrimido[4,5-c]pyridazine-5,7-dione (**10**) was the principal product. In addition an acid, ($C_6H_4N_4O_3 \cdot H_2O$)(**11**) of unknown structure was isolated. The structure of pyrimido[4,5-c]pyridazine-5,7-dione (**10**) was established by the alkaline ring opening reaction to give 3-aminopyridazine-4-carboxylic acid (**12**), a new compound. We have proven the structure of 3-aminopyridazine-4-carboxylic acid (**12**) by the unequivocal synthesis of 4-aminopyridazine-3-carboxylic acid (**15**) from 4-amino-3-cyanopyridazine (**16**), whose constitution will be discussed at a later point in this paper. Compounds **12** and **15** are not identical, thus the constitution of both **10** and **12** are established. Compound **11** was decarboxylated and compound **14**, $C_5H_4N_4O$ was obtained. The constitution of **14** has not been established. Attempts to chlorinate pyrimido[4,5-c]pyridazine-5,7-dione (**10**) with phosphorus oxychloride or phosphorus oxychloride-phosphorus pentachloride mixtures has been unsuccessful. A compound with the properties expected of 5,7-dichloropyrimido[4,5-c]pyridazine (**13**) was not isolated. These transformations are recorded in Flow Sheet II.

Flow Sheet II



The synthetic steps required for synthesis and structure proof of 3-methylpyrimido[4,5-c]pyridazine-5-one (**21**) are outlined in Flow Sheet III. Ethyl 3-chloro-6-methylpyridazine-4-carboxylate (**17**) (6) was treated with saturated methanolic ammonia in a rocking autoclave. Three products were obtained, namely, 3-amino-6-methylpyridazine-4-carboxamide (**18**), 3-methoxy-6-methylpyridazine-4-carboxamide (**19**) and 3-methylpyridazin-6-one-5-carboxamide (**20**). Compound **19** and **20** were characterized from the analytical data and by spectral means. The reaction of 3-amino-6-methylpyridazine-4-carboxamide (**18**) with ethyl orthoformate gave 3-methylpyrimido-[4,5-c]pyridazin-5-one (**21**). The structure of **21** is evident from the synthetic route, however, the ultraviolet and infrared spectra are also consistent with the assigned structure. Treatment of 3-methylpyrimido[4,5-c]pyridazin-5-one (**21**) with aqueous sodium hydroxide gave 3-amino-6-methylpyridazine-4-carboxylic acid (**5**). The acid (**5**) was smoothly esterified with methanol to give methyl 3-amino-6-methylpyridazine-4-carboxylate (**22**) which, upon treatment with saturated methanolic ammonia gave 3-amino-6-methylpyridazine-4-carboxamide (**18**).

Flow Sheet III

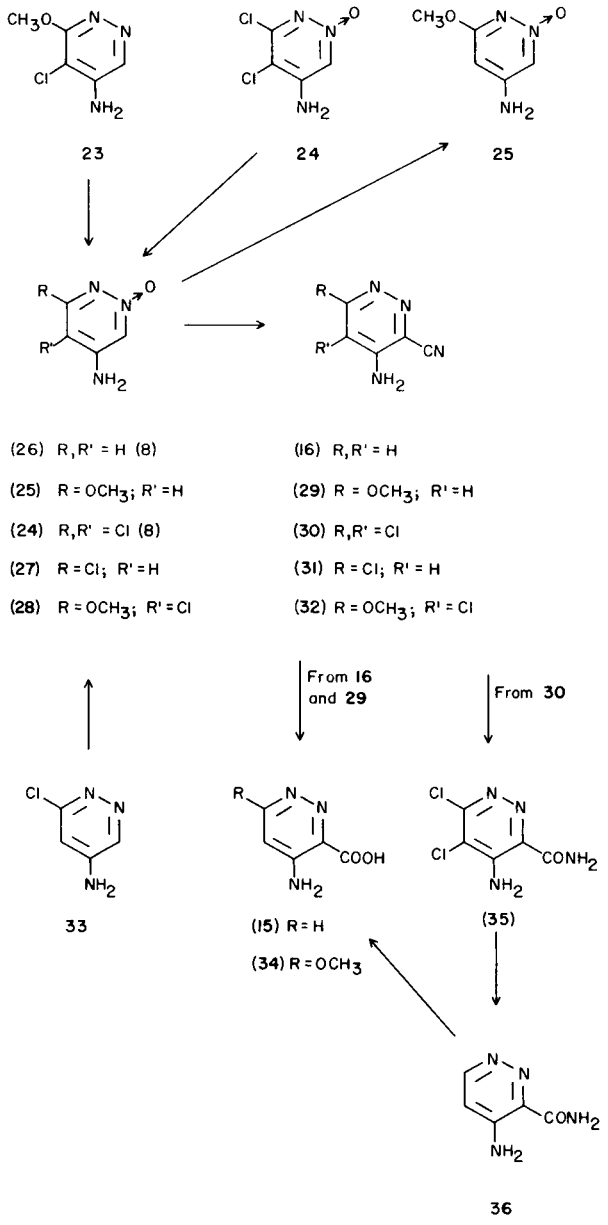


In order to provide a series of aminocyanopyridazines and aminopyridazinecarboxamides for further cyclization studies, the sequence of reactions in Flow Sheet IV was carried out.

5-Aminopyridazine 1-oxide (**26**) (7) was subjected to a modified Reissert reaction (8-10) using dimethyl sulfate followed by treatment with aqueous potassium cyanide. The product, 4-amino-3-cyanopyridazine (**16**), was hydrolyzed with aqueous sodium hydroxide into 4-aminopyridazine-3-carboxylic acid (**15**).

5-Amino-3,4-dichloropyridazine 1-oxide (**24**) (7) was converted into 4-amino-3-cyano-5,6-dichloropyridazine (**30**) via the modified Reissert reaction. The cyano group must enter position 3 of compound **24** since this is the only position available. It was possible to establish that the cyano group in **16** was also present on the 3-position by the following reaction: 4-amino-3-cyano-5,6-dichloropyridazine (**30**) was hydrolyzed with concentrated sulfuric acid into 4-amino-5,6-dichloropyridazine-3-carboxamide (**35**); compound **35** was catalytically dechlorinated with palladium on charcoal in ammonium hydroxide suspen-

Flow Sheet IV



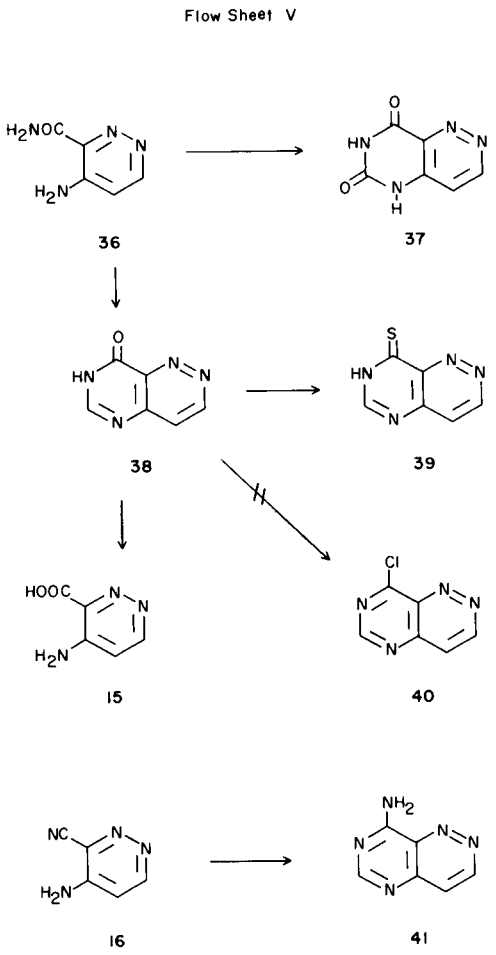
sion to give 4-aminopyridazine-3-carboxamide (**36**) which was readily hydrolyzed into 4-aminopyridazine-3-carboxylic acid (**15**), identical in all respects with 15 prepared as described above.

Three additional pyridazine 1-oxides were subjected to the modified Reissert reaction to produce the corresponding aminocyanopyridazines. Thus, 5-amino-3-methoxypyridazine 1-oxide (**25**) gave 4-amino-3-cyano-6-methoxypyridazine (**29**); 5-amino-3-chloropyridazine 1-oxide (**27**) gave 4-amino-6-chloro-3-cyanopyridazine (**31**); and 5-amino-4-chloro-3-methoxypyridazine 1-oxide (**28**) gave 4-amino-5-chloro-3-cyano-6-methoxypyridazine (**32**). The position of the cyano group in compounds **29** and **31** was assigned by analogy. The spectral data for all of the nitriles prepared are consistent with the structures assigned.

5-Amino-4-chloro-3-methoxypyridazine 1-oxide (**28**) was obtained from 5-amino-4-chloro-3-methoxypyridazine (**23**) (11) by *N*-oxidation. Compound **28** was also obtained from 5-amino-3,4-dichloropyridazine 1-oxide (**24**) (7) by the action of methanolic potassium hydroxide. The catalytic dechlorination of 5-amino-4-chloro-3-methoxypyridazine 1-oxide (**28**) gave 5-amino-3-methoxypyridazine 1-oxide (**25**). 5-Amino-3-chloropyridazine (**33**) (11) upon *N*-oxidation gave 5-amino-3-chloropyridazine 1-oxide (**27**). The structures of **25** and **28** are apparent from the synthetic methods. The structure of **27** was assigned by analogy with 5-amino-3,4-dichloropyridazine 1-oxide (7).

For the synthesis of members of the novel pyrimido[5,4-c]pyridazine ring system 4-amino-3-cyanopyridazine (**16**) and 4-aminopyridazine-3-carboxamide (**36**) served as starting materials. 4-Aminopyridazine-3-carboxamide (**36**) when fused with urea gave pyrimido[5,4-c]pyridazine-6,8-dione (**37**). Treatment of 4-aminopyridazine-3-carbox-

Flow Sheet V



amide (**36**) with ethyl orthoformate yielded pyrimido[5,4-*c*]pyridazin-8-one (**38**). Pyrimido[5,4-*c*]pyridazine-8-thione (**39**) was obtained upon phosphorus pentasulfide thiation of pyrimido[5,4-*c*]pyridazin-8-one (**38**). Attempts to chlorinate pyrimido[5,4-*c*]pyridazin-8-one (**38**) with phosphorus oxychloride or phosphorus oxychloride-phosphorus pentachloride mixtures were unsuccessful. A product with the properties expected of 8-chloropyrimido[5,4-*c*]pyridazine (**40**) was not obtained. 4-Amino-3-cyanopyridazine (**16**) was cyclized with formamide into 8-aminopyrimido[5,4-*c*]pyridazine (**41**).

EXPERIMENTAL (12)

The Hofmann Reaction of 6-Methylpyridazine-3,4-dicarboxamide (**1**).

3-Methylpyrimido[4,5-*c*]pyridazine-5,7-dione (**2**) and 3-Methylpyrimido[5,4-*c*]pyridazine-6,8-dione (**3**).

6-Methylpyridazine-3,4-dicarboxamide (**1**) (3) (2.5 g., 0.014 mole) was added all at once to a stirred solution containing 9.5 g. (0.145 mole) of potassium hydroxide, 4.5 g. (0.028 mole) of bromine in 23 ml. of water and 55 g. of crushed ice. The diamide quickly dissolved. After the reaction mixture was allowed to stand overnight in the refrigerator, it was heated on the steam bath for one hour, followed by acidification with acetic acid. The crystalline product which separated was collected, washed with water and dried, yielding 1.43 g. of a crude mixture of compounds **2** and **3**, m.p. $>300°$. Concentration of the filtrate under reduced pressure to a small volume gave a yellow crystalline solid which was separated by filtration and recrystallized from water and then recrystallized from methanol to give 0.6 g. of yellow needles, m.p. 323-324° dec. (potassium salt). This product was dissolved in water and acidification with concentrated hydrochloric acid precipitated orange needles, m.p. 291° dec., yield 0.5 g. (19%). This acidic product (**4**) of unknown structure had the following spectral data; U. V. λ max (95% ethanol), 226 (ϵ, 19,200), 349 mμ (ϵ, 700); infrared cm^{-1}, 3480(s), 3280 broad(s), 3050(s), 3000~2700 broad(m), 2600~2200 broad(m), 1900 broad(w), 1715(s), 1675(s), 1625(m), 1575(m), 1525(m), 1425(m), 1415(m), 1390(m), 1310(s), 1230 broad(s), 1150(w), 1080(w), 1035(w), 968(w), 930(w), 848(m), 783(m), 760(w), 710 broad(m), 675(m), 610(w), 500(m); NMR spectrum (dimethylsulfoxide-d_6), 7.38 δ (ring-H, singlet), 2.34 δ (C-CH_3, singlet); (deuterium oxide-potassium carbonate), 7.09 δ (ring-H, singlet), 2.43 δ (C-CH_3, singlet).

Anal. Calcd. for $C_7H_6N_4O_3$: C, 43.31; H, 3.12; N, 28.86. Found: C, 42.93; H, 3.23; N, 29.25; Molecular weight, Calcd: 194. Found: 200 (osmometer).

The crude mixture consisting of **2** and **3** was digested with 500 ml. of hot methanol and filtered while hot. The insoluble material was recrystallized from water, yielding 0.2 g. (8%) of 3-methylpyrimido[5,4-*c*]pyridazine-6,8-dione (**3**) as colorless crystals, m.p. $>300°$; U. V. λ max (95% ethanol), 214 (ϵ, 28,700), 250 (ϵ, 6,500), 296 mμ (ϵ, 4,100); infrared cm^{-1}, 3210(m), 3170(m), 3075(s), 3020(m), 2810 broad(m), ~2500 broad envelope, 1735(s), 1705(s), 1610(s), 1575(m), 1445(m), 1375(s), 1360(m), 1300(s), 1277(m), 1214(m), 1158(w), 1135(w), 1050(m), 928(w), 898(w), 845(w), 824(m), 802(w), 744(w), 733(m), 707(w), 630(w), 551(m), 482(w), 448(m).

Anal. Calcd. for $C_7H_6N_4O_2$: C, 47.19; H, 3.40; N, 31.45. Found: C, 47.43; H, 3.62; N, 31.26.

The methanol filtrate was evaporated to dryness and thrice recrystallized from hot water. There was obtained 1.1 g. (45%) of colorless leaflets of 3-methylpyrimido[4,5-*c*]pyridazine-5,7-dione (**2**), m.p. $>350°$.

Anal. Calcd. for $C_7H_6N_4O_2 \cdot 3/4H_2O$: C, 43.86; H, 3.94; N, 29.32. Found: C, 43.76; H, 4.43; N, 29.56.

The water of crystallization was removed by heating at 100° overnight *in vacuo;* U. V. λ max (95% ethanol), 218 (ϵ, 23,300), shoulder 232 (ϵ, 11,950), 330 mμ (ϵ, 4,000); infrared cm^{-1}, 3190(s), 3090(s), 3050(s), 2960(m), 2870(m), 2830(m), ~2500 broad(m), 1730(s), 1680(s), 1620(m), 1565(m), 1500(m), 1425(s), 1390(s), 1375(m), 1340(m), 1300(s), 1258(m), 1230(m), 1220(m), 1143(m), 1116(w), 1013(m), 954(w), 942(m), 877(w), 845(m), 798(m), 750(m), 710(w), 670(m), 630(w), 560(m), 502(s), 442(s).

Anal. Calcd. for $C_7H_6N_4O_2$: C, 47.19; H, 3.40; N, 31.45. Found: C, 47.39; H, 3.70; N, 31.27.

Decarboxylation of the Unknown Acid (**4**).

The acid of unknown structure (**4**) (0.5 g., 0.00258 mole) was heated at its melting point (280-285°) until the melt solidified (~3-5 minutes). After cooling, the product was dissolved in hot water, treated with Norite and filtered. Evaporation of the filtrate under reduced pressure and recrystallization of the residue from absolute ethanol yielded 0.3 g. of light yellow needles, m.p. 290-291° and 0.05 g. of a second crop, m.p. 290° for a total yield of 91%: U. V. λ max (95% ethanol), 221 (ϵ, 21,900), shoulder 242 (ϵ, 1,700), 344 mμ (ϵ, 950); [95% ethanol + 1*N* sodium hydroxide (99:1)], 238 mμ (ϵ, 14,250); (water), 217 (ϵ, 19,700), shoulder 238 (ϵ, 1,800), 330 mμ (ϵ, 1,300); infrared cm^{-1}, 3180(s), 3150 broad(s), 2900(m), 2825(m), 2775(m), ~2600 broad envelope, 1700(s), 1640(m), 1620(m), 1555(s), 1520(m), 1450(w), 1430(m), 1395(w), 1380(m), 1350(s), 1320(w), 1273(w), 1245(w), 1153(m), 1135(w), 1080(m), 1035(w), 930(m), 830(m), 770(w), 742(m), 722(w), 696(w), 608(m), 598(w), 484(w); NMR spectrum (dimethylsulfoxide-d_6), 7.57 δ (doublet, J=9.6), 6.88 δ (doublet, J=9.8), 2.27 δ (C-CH_3, singlet).

Anal. Calcd. for $C_6H_6N_4O$: C, 48.00; H, 4.03; N, 37.32. Found: C, 48.26; H, 4.17; N, 37.21. Molecular weight, Calcd: 150. Found: 147 (osmometer).

3-Amino-6-methylpyridazine-4-carboxylic Acid (**5**).

Method A.

A solution containing 0.4 g. (0.0025 mole) of 3-methylpyrimido[4,5-*c*]pyridazine-5,7-dione (**2**) in 20 ml. of 10% aqueous sodium hydroxide was heated in a sealed tube at 170-180° (oil bath) for 3 hours. After cooling, the filtered solution was acidified to *p*H 2.5 with concentrated hydrochloric acid. The crystalline material which separated was collected by filtration and recrystallized from water, yielding 0.2 g. (58%) of colorless leaflets, m.p. 288° dec.; U. V. λ max (95% ethanol), 211 (ϵ, 15,600), 236 (ϵ, 6,800), 323 mμ (ϵ, 2,300); infrared cm^{-1}, 3280(s), 2950 broad(s), 2720(m), ~2200 broad envelope, 1960 broad(m), 1700(s), 1625(m), 1575(s), 1450(m), 1360(s), 1255(m), 1210(w), 1109(m), 1050(w), 997(m), 952(w), 815(m), 780(s), 680(s).

Anal. Calcd. for $C_6H_7N_3O_2$: C, 47.06; H, 4.61; N, 27.44. Found: C, 47.54; H, 4.89; N, 27.46.

Method B.

A solution containing 0.35 g. (0.002 mole) of 3-methylpyrimido[4,5-*c*]pyridazine-5,7-dione (**2**) in 7 ml. of concentrated sulfuric acid was heated at 200-210° for 2 hours. The reaction mixture was cooled to room temperature, poured into ice, was made alkaline with sodium bicarbonate and concentrated under

reduced pressure. The inorganic salts were removed by filtration and the *p*H was adjusted to 3 by the addition of concentrated hydrochloric acid. The solid was removed by filtration and recrystallized from methanol, yielding 0.04 g. (13%) of 3-amino-6-methylpyridazine-4-carboxylic acid (**5**), m.p. 285° dec., undepressed on admixture with the sample prepared by Method A. The infrared spectra of these two samples were identical.

3-Amino-6-methylpyridazine (**6**).

3-Amino-6-methyl-4-pyridazinecarboxylic acid (0.025 g., 0.00016 mole) was mixed with 0.025 g. of copper powder in a small test tube. The tube was heated with an open flame until gas evolution ceased. The sublimate was dissolved in water and the solution was filtered and evaporated to dryness *in vacuo*. Recrystallization of the residue from ethyl acetate gave 0.012 g. (67%) of colorless leaflets, m.p. 224-225°. No depression of the melting point was observed when mixed with an authentic sample of 3-amino-6-methylpyridazine (**4**). The infrared spectra of both samples were identical.

The Hofmann Reaction of Pyridazine-3,4-dicarboxamide (**9**). Pyrimido[4,5-c]pyridazine-5,7-dione (**10**).

Pyridazine-3,4-dicarboxamide monohydrate (**9**) (4 g., 0.022 mole) was added all at once to a stirred solution containing 7 g., (0.044 mole) of bromine, 13.5 g. (0.19 mole) of potassium hydroxide, 40 ml. of water and 100 g. of crushed ice. The diamide dissolved quickly. After the reaction mixture was allowed to stand overnight in the refrigerator, the solution was heated for one hour on the steam bath, followed by acidification with acetic acid. The crystalline product which separated was collected, washed with water and dried in air, yield 1.5 g. (39%), m.p. 335° dec. Recrystallization from methanol gave 1.15 g. (30%) of hydrated pyrimido[4,5-c]pyridazine-5,7-dione (**10**) in the form of colorless prisms, m.p. 356° dec.; U. V. λ max (95%) ethanol), 215 (ε, 27,700), 230 shoulder (ε, 9,800), 322 mμ (ε, 3,600); infrared cm^{-1}, 3160(m), 3025 broad(s), 2925(m), 2800(m), ~2500 broad, 1735(s), 1720(s), 1700(s), 1610(s), 1575(m), 1475(m), 1400(s), 1330(m), 1280(m), 1160(m), 1120(w), 1050(w), 995(w), 927(w), 870(w), 800(m), 708(w), 655(w), 578(w), 485(s), 455(w).

Anal. Calcd. for $C_6H_4N_4O_2$: C, 43.91; H, 2.46; N, 34.14. Found: C, 43.88; H, 2.58; N, 34.40.

Isolation of an Acid of Unknown Structure (**11**)

The aqueous filtrate from pyrimido[4,5-c]pyridazine-5,7-dione was concentrated under reduced pressure and cooled. The yellow prisms that separated were collected by filtration, m.p. 337° dec., yield 1.25 g. Acidification of the filtrate with hydrochloric acid precipitated a yellow solid, which was filtered and washed with water, m.p. 273°, yield 0.45 g.

A part of the yellow prisms (0.6 g.), m.p. 337° dec., was dissolved in a minimum amount of water and acidified with hydrochloric acid.

The precipitate was filtered, washed with water and air dried to give 0.55 g. (total yield, 27%) of the yellow crystals, m.p. 273° dec. This was recrystallized from water to afford yellow prisms, m.p. 292° dec.; U. V. λ max (95% ethanol), 218 mμ (95% ethanol + 1 *N* sodium hydroxide, 2 drops), 240 mμ (ε, 23,000); infrared cm^{-1}, 3275 broad(s), 3120 broad(s), 3050(s), 2890(s), 2825(m), 2500~2150 broad(w), 1900(w), 1730(s), 1695(s), 1560(m), 1525(w), 1450(m), 1390(m), 1300(s), 1283(m), 1270(s), 1227(m), 1185(m), 1103(w), 1040(w), 1005(w), 966(w), 890(w), 882(m), 783(m), 765(w), 740(m), 690(m), 617(m), 590(m), 430(m).

Anal. Calcd. for $C_6H_4N_4O_3 \cdot H_2O$: C, 36.37; H, 3.05; N, 28.28. Found: C, 36.84; H, 3.25; N, 28.92.

The compound retains water of crystallization after heating at 100° for 48 hours *in vacuo*.

Decarboxylation of the Unknown Acid (**11**).

The acid of unknown structure (**11**) (0.9 g., 0.00455 mole) was heated at 270-280° (oil bath) until evolution of gas subsided (~2-3 minutes). After cooling, the product was dissolved in hot water, treated with Norite and filtered. The filtrate was evaporated to dryness *in vacuo*, and the residue recrystallized from ethanol, giving light yellow needles, m.p. 265-266°, yield 0.4 g. From the filtrate 0.15 g. of a second crop was obtained by concentration, m.p. 264-265°, total yield, 0.55 g. (89%) of unknown compound **14**; U. V. λ max (95% ethanol), 216 (ε, 17,800), 245 (ε, 1,800), 347 mμ (ε, 800); [95% ethanol + 1 *N* sodium hydroxide (99:1)], 235 mμ (ε, 8,200); (water), 212 (ε, 19,000), 240 (ε, 1,900), 336 mμ (ε, 1,000); infrared cm^{-1}, 3180(s), 3075(s), 2875(m), 2810(m), 1710(s), 1620(m), 1550(s), 1520(m), 1440(w), 1420(w), 1395(w), 1365(s), 1325(m), 1315(m), 1300(m), 1225(m), 1170-1130 broad(w), 1080(m), 1000(w), 912(s), 905(m), 810(s), 880-775 broad(m), 738(m), 690(m), 583(w), 577(w), 540(m).

Anal. Calcd. for $C_5H_4N_4O$: C, 44.12; H, 2.96; N, 41.16. Found: C, 43.87; H, 2.81; N, 41.38.

3-Aminopyridazine-4-carboxylic Acid (**12**).

A solution containing 0.5 g. (0.00275 mole) of hydrated pyrimido[4,5-c]pyridazine-5,7-dione (**10**) and 20 ml. of 10% aqueous sodium hydroxide was heated in a pressure bottle for 3 hours at 150-160°. After cooling, the filtered solution was adjusted to *p*H 2.0-2.5 by the addition of concentrated hydrochloric acid. The crystalline solid that separated was filtered and purified by recrystallization from water. The colorless needles thus obtained melt at 261-262° dec., yield 0.3 g. (79%); U. V. λ max (95% ethanol), 208 (ε, 18,600), 235 (ε, 8,200), 325 mμ (ε, 2,600); infrared cm^{-1}, 3290(s), 2950 broad(m), 2700-2200 broad(m), 1950(w), 1695(s), 1630(m), 1560(m), 1425(w), 1350(s), 1325(s), 1290(w), 1180(m), 1061(m), 1037(w), 880(w), 805(m), 720(w), 670(s), 593(m), 545(w).

Anal. Calcd. for $C_5H_5N_3O_2$: C, 43.17; H, 3.62; N, 30.21. Found: C, 42.83; H, 3.68; N, 29.89.

The Reaction of Ethyl 3-Chloro-6-methylpyridazine-4-carboxylate (**17**) with Methanolic Ammonia.

The Preparation of 3-Amino-6-methylpyridazine-4-carboxamide (**18**), 3-Methoxy-6-methylpyridazine-4-carboxamide (**19**) and 3-Methylpyridazine-5-carboxamide-6-one (**20**).

Ethyl 3-chloro-6-methylpyridazine-4-carboxylate (**17**)(6) (7 g., 0.035 mole) in 140 ml. of saturated (at 0°) methanolic ammonia was heated in a rocking autoclave at 120-130° for 24 hours. The reaction mixture was evaporated to dryness and the residue was repeatedly extracted with boiling acetone. The extract was filtered and concentrated and a solid separated which was removed by filtration. (fraction A). The acetone filtrate was evaporated to dryness and the dried residue was extracted with boiling benzene. The undissolved residue was separated by filtration and combined with fraction A. The benzene filtrate was evaporated to dryness the residue was recrystallized from benzene to give 1.6 g. (28%) of 3-methoxy-6-methylpyridazine-4-carboxamide (**19**) as colorless plates, m.p. 155-156°; U. V. λ max (95% ethanol), shoulder 211 (ε, 7,500), 291 mμ (ε, 2,450); infrared cm^{-1}, 3340 broad(s), 3125 broad(s), 2970(m), 2825(w), 1680(s), 1620(s), 1610(m), 1540(w), 1480(s), 1455(m), 1425(s), 1390(s), 1345(m), 1305(s), 1225(w), 1190(w), 1146(w), 1131(m), 1038(w), 1013(s), 930(w),

920(w), 796(m), 780(w), 722(m), 650(m), 633(m), 500(m), 433(w).

Anal. Calcd. for $C_7H_9N_3O_2$: C, 50.30; H, 5.43; N, 25.14. Found: C, 50.19; H, 5.23; N, 25.06.

The acetone and benzene insoluble materials (fraction A) were washed with a small amount of cold water, dried and fractionally recrystallized from methanol or ethanol to yield 0.35 g. (7%) of pale yellow rhombs, m.p. 253-255°, undepressed on admixture with an authentic sample of 3-amino-6-methylpyridazine-4-carboxamide (**18**) prepared from methyl 3-amino-6-methylpyridazine-4-carboxylate (**22**). Both samples of **18** have identical infrared spectra.

From the fractional recrystallization process described above, there was obtained 0.3 g. (6%) of 3-methylpyridazine-5-carboxamide-6-one (**20**) as colorless needles, m.p. 282-283°; U. V. λ max (95% ethanol), 208 (ε, 15,800), 224 shoulder (ε, 5,300); 325 mμ (ε, 3,200); infrared cm^{-1}, 3470 broad(s), 3175 broad(s), 2970(m), 2890(m), 1700(s), 1650(m), 1600(s), 1575(s), 1460(m), 1390(m), 1225(m), 1197(w), 1085(m), 1040(w), 995(w), 940(w), 920(m), 817(m), 803(m), 715(w), 590(s), 505(m).

Anal. Calcd. for $C_6H_7N_3O_2$: C, 47.06; H, 4.61; N, 27.44. Found: C, 47.32; H, 4.41; N, 27.42.

In another experiment where the reaction conditions were the same except the reaction temperature was increased to 130-140° and the work-up of the residue was modified, a different proportion of the products was obtained.

The reaction mixture was evaporated to dryness, the residue was washed with a small amount of cold water and filtered. The solid was treated with cold, dilute, aqueous sodium hydroxide solution and the crude insoluble 3-amino-6-methylpyridazine-4-carboxamide (**18**) was collected by filtration. Neutralization of the filtrate with concentrated hydrochloric acid to *p*H 7.0 precipitated 3-methylpyridazine-5-carboxamide-6-one (**20**) which was filtered and washed with water (fraction A). The filtrate was concentrated *in vacuo* and the crystalline material which separated was treated again with cold, dilute, aqueous sodium hydroxide solution, filtered and an additional amount of the aminocarboxamide (**18**) was obtained. The filtrate (B) which contained more of fraction A was worked up as described below. The combined crude **18** was recrystallized from methanol to yield 1.2 g. (11%) of pale yellow needles of m.p. 254-255°, undepressed on admixture with an authentic sample prepared from methyl 3-amino-6-methylpyridazine-4-carboxylate (**22**).

The filtrate (B) was neutralized with concentrated hydrochloric acid and the solid which separated was collected and combined with fraction A. This material was recrystallized from water, giving 2.5 g. (22%) of 3-methylpyridazine-5-carboxamide-6-one (**20**) as colorless needles, m.p. 282-283° undepressed on admixture with the sample prepared as described above.

3-Methylpyrimido[4,5-*c*]pyridazin-5-one (**21**).

A mixture of 0.3 g. (0.002 mole) of 3-amino-6-methylpyridazine-4-carboxamide and ethyl orthoformate was stirred and refluxed for 6 hours. After cooling, the insoluble crystalline solid was filtered, washed with ether and dried to give 0.25 g. (78%) of 3-methylpyrimido[4,5-*c*]pyridazin-5-one (**21**) m.p. >300°. The analytical sample was recrystallized from methanol, colorless needles, m.p. >300°, yield, 0.15 g., U. V. λ max (95% ethanol), 263 (ε, 7,900), 319 mμ (ε, 4,400); infrared cm^{-1}, 3175(m), 3070(s), 2900 broad(m), 2620(w), 1700(s), 1610(s), 1595(m), 1540(m), 1420(s), 1380(m), 1370(w), 1280(s), 1230(w), 1204(w), 1142(m), 1092(w), 1035(w), 938(w), 918(w), 894(m), 816(s), 757(w), 742(w), 730(w), 608(m), 590(w), 580(w), 542(w), 522(m), 495(w), 458(w).

Anal. Calcd. for $C_7H_6N_4O$: C, 51.85; H, 3.73; N, 34.55. Found: C, 51.63; H, 3.84; N, 34.60.

3-Amino-6-methylpyridazine-4-carboxylic Acid (**5**).

For structure proof of 3-methylpyrimido[4,5-*c*]pyridazin-5-one (**21**) it was ring-opened to **5**.

Fifty mg. (0.31 mmole) of 3-methylpyrimido[4,5-*c*]pyridazin-5-one (**21**) was dissolved in 0.6 ml. of deuterium oxide containing a small amount of sodium deuterioxide and the solution was allowed to stand at room temperature for one week. The NMR spectrum was observed periodically. The peaks at 8.35 δ, 7.79 δ (ring protons, singlets) and 2.66 δ ($-CH_3$, singlet) diminished gradually and a new peak at 7.49 δ (ring proton singlet) and 2.35 δ (CH_3, singlet) appeared. At the end of one week the *p*H of the solution was adjusted to ~2-2.5 by the addition of concentrated hydrochloric acid. The precipitated crystalline material was filtered, washed with a small amount of water and dried, m.p. 288° dec., undepressed on admixture with an authentic sample of 3-amino-6-methylpyridazine-4-carboxylic acid (**5**). The infrared spectra of both samples were identical.

Methyl 3-Amino-6-methylpyridazine-4-carboxylate (**22**).

To 20 ml. of methanol containing 1.2 g. (0.033 mole) of gaseous hydrogen chloride was added 1.5 g. (0.01 mole) of 3-amino-6-methylpyridazine-4-carboxylic acid and the resulting mixture was refluxed for 6.5 hours. The solvent was removed by distillation, the residue poured into cold water and the solution made alkaline with sodium bicarbonate with ice cooling. The precipitated ester was filtered, washed with aqueous sodium bicarbonate solution and then water. After being dried, the product weighed one g. (61%), m.p. 172-173°. An analytical sample was prepared by recrystallization from water to colorless needles and drying at 75° overnight *in vacuo*, m.p. 185° dec., yield 0.83 g. (51%); U. V. λ max (95% ethanol), 218 (ε, 11,600), 241 (ε, 7,650), 357 mμ (ε, 3,300); infrared cm^{-1}, 3430(s), 3280(m), 3220(m), 3155(m), 2965(w), 1715(s), 1625(s), 1585(s), 1550(m), 1445(s), 1435(s), 1390(w), 1365(w), 1330(m), 1290(s), 1228(m), 1142(s), 1097(m), 995(m), 918(w), 906(w), 802(m), 785(w), 720(w), 690(w), 574(m), 537(m), 502(w).

Anal. Calcd. for $C_7H_9N_3O_2$: C, 50.30; H, 5.43; N, 25.14. Found: C, 50.16; H, 5.47; N, 25.23.

Ammonolysis of Methyl 3-Amino-6-methylpyridazine-4-carboxylate (**22**).

3-Amino-6-methylpyridazine-4-carboxamide (**18**).

To 50 ml. of methanol saturated with ammonia was added 0.45 g. (0.0027 mole) of methyl 3-amino-6-methylpyridazine-4-carboxylate (**22**) and the resulting solution was allowed to stand at room temperature overnight in a tightly stoppered flask. When the solution was concentrated to a small volume, the crystalline solid precipitated and was collected by filtration, m.p. 255°; yield 0.3 g. (73%). An analytical sample was recrystallized from methanol, pale yellow needles, m.p. 255°; U. V. λ max (95% ethanol), 212 (ε, 13,800), 242 (ε, 9,000), 346 mμ (ε, 2,500); infrared cm^{-1}, 3470(s), 3370(s), 3290(s), 3115 broad(s), 1680(s), 1640(s), 1580(s), 1455(s), 1420(s), 1385(m), 1315(w), 1164(s), 1126(w), 1105(w), 1060(w), 1040(w), 987(w), 934(w), 906(w), 798(w), 738(m), 656(s), 547(m), 504(m), 444(w).

Anal. Calcd. for $C_6H_8N_4O$: C, 47.36; H, 5.30; N, 36.82. Found: C, 47.26; H, 5.46; N, 37.03.

5-Amino-4-chloro-3-methoxypyridazine 1-Oxide (**28**) by Oxidation of 5-Amino-4-chloro-3-methoxypyridazine (**23**).

A solution containing 11 g. (0.069 mole) of 5-amino-4-chloro-3-methoxypyridazine (**23**) (11), 7.7 ml. of 30% hydrogen peroxide

and 60 ml. of acetic acid was heated at 60-65°. After 3 hours, the solution was mixed with a further 7.7 ml. of 30% hydrogen peroxide and kept at the same temperature for an additional 7 hours. The resulting solution was evaporated under reduced pressure, diluted with water and again evaporated to a small volume. The residue was cooled with ice water, made alkaline with aqueous sodium hydroxide solution and the insoluble solid was filtered, washed with a small quantity of cold water and dried to give 8.7 g. (72%) of 5-amino-4-chloro-3-methoxypyridazine 1-oxide, m.p. 242° dec. Recrystallization from ethanol gave colorless needles, m.p. 249° dec.; U. V. λ max (95% ethanol), 218 (ε, 16,000), 243 (ε, 24,000), 289 mμ (ε, 10,100); infrared cm^{-1}, 3650~3300 broad(m), 3166(m), 1638(s), 1583(s), 1553(w), 1500(m), 1460(m), 1450(w), 1400(s), 1380(s), 1260(w), 1227(s), 1200(m), 1155(m), 1004(w), 1000(w), 961(m), 827(w), 730(m), 668(w), 630(w), 550(w).

Anal. Calcd. for $C_5H_6ClN_3O_2$: C, 34.19; H, 3.44; N, 23.93. Found: C, 34.18; H, 3.63; N, 23.67.

The aqueous alkaline filtrate from the *N*-oxide (**28**) was acidified with dilute hydrochloric acid and allowed to stand overnight. The 4-amino-5-chloro-6-pyridazinone (**42**) (13) which separated was removed by filtration, m.p. >300°, yield 0.7 g. (7%). It was recrystallized from water to colorless needles. The infrared spectrum was identical to that of an authentic speciman (13).

5-Amino-4-chloro-3-methoxypyridazine 1-Oxide (**28**) from 5-Amino-3,4-dichloropyridazine 1-Oxide (**24**).

To a methanolic solution of 0.42 g. (0.0064 mole) of potassium hydroxide was added 0.9 g. (0.005 mole) of 5-amino-3,4-dichloropyridazine 1-oxide (**24**) (7) and the mixture was heated under reflux for one hour. The methanol was distilled off under reduced pressure, the residue was diluted with water and the insoluble solid was collected by filtration, yield 0.8 g. (91%). Recrystallization from methanol gave colorless needles, m.p. 252° dec., undepressed when mixed with a sample of 5-amino-4-chloro-3-methoxypyridazine 1-oxide prepared by the oxidation of 5-amino-4-chloro-3-methoxypyridazine (**23**), yield, 0.57 g. (65%).

5-Aminopyridazine 1-Oxide (**26**) (7).

When the reduction was carried out according to Sako (7), a considerable amount of 5-amino-3-methoxypyridazine 1-oxide was produced together with the desired 5-aminopyridazine 1-oxide. Therefore, methanolic sodium hydroxide was replaced by aqueous ammonia in the following reduction.

A mixture containing 30 g. (0.17 mole) of 5-amino-3,4-dichloropyridazine 1-oxide (**24**) (7), 60 ml. of 28% aqueous ammonia, 200 ml. of water and 4 g. of 5% palladium on charcoal was shaken with hydrogen. The reduction was stopped when 2 molecular equivalents of hydrogen were absorbed and the catalyst was removed by filtration. Sodium hydroxide (16 g.) was dissolved in the filtrate and the solution was evaporated to a small volume. The solution was neutralized with hydrochloric acid to *p*H 7, evaporated to dryness under reduced pressure, and the dried residue was extracted with boiling ethanol. When the extracts were concentrated and cooled, 5-aminopyridazine 1-oxide separated, weighing 11.95 g. (65%), m.p. 190-191° (Lit. (7) 188.5-190°).

5-Amino-3-methoxypyridazine 1-Oxide (**25**).

A mixture of 10 g. (0.057 mole) of 5-amino-4-chloro-3-methoxypyridazine 1-oxide, 2 g. of palladium-charcoal and 100 of ml. of methanolic sodium hydroxide containing 3 g. of sodium hydroxide and a small amount of water to dissolve the sodium hydroxide, was shaken with hydrogen at atmospheric pressure. One equivalent of hydrogen was absorbed. After removal of the catalyst by filtration, the filtrate was neutralized with hydrochloric acid to *p*H 7 and evaporated under reduced pressure to dryness. The residue was dissolved in a chloroform-methanol mixture (2:1) and the solution was passed through an alumina column for decolorization. Evaporation of the eluate left crude 5-amino-3-methoxypyridazine 1-oxide which was recrystallized from water, yielding colorless needles, m.p. 172-173°. After drying at 70-80° *in vacuo* overnight, the product melted at 173-174°, yield, 7 g. (87%); U. V. λ max (95% ethanol), 217 (ε, 15,600), 239 (ε, 21,700), 283 (ε, 6,700), shoulder 298 mμ (ε, 4,100); infrared cm^{-1}, 3355 broad(s), 3305 broad(s), 3190(s), 3095(w), 3000(w), 2945(w), 1625(s), 1585(s), 1545(s), 1485(m), 1445(s), 1435(s), 1410(s), 1240~1205 broad(s), 1123(w), 1095(w), 1062(m), 1038(m), 962(m), 816(m), 708(w), 665(m), 633(m), 604(w), 551(w), 528(w).

Anal. Calcd. for $C_5H_7N_3O_2$: C, 42.55; H, 5.00; N, 29.70. Found: C, 42.77; H, 5.03; N, 29.69.

5-Amino-3-chloropyridazine 1-Oxide (**27**).

A mixture containing 3 g. (0.023 mole) of 5-amino-3-chloropyridazine (**33**), 22.5 ml. of acetic acid and 2.25 ml. of 30% hydrogen peroxide was heated at 65° for 45 minutes. An additional 2.25 ml. of 30% hydrogen peroxide was added and the mixture was heated at the same temperature for 14 hours. The reaction mixture was concentrated *in vacuo* to a small volume, diluted with water and again concentrated. Orange prisms which precipitated were collected, washed with a small amount of water and dried. There was obtained 2.4 g. (72%) of the crude product. After recrystallization from water with Norite treatment, pure 5-amino-3-chloropyridazine 1-oxide was obtained as colorless prisms, m.p. 215-216.5°, yield 1.6 g. (48%); U. V. λ max (95% ethanol), 208 (ε, 7,800), 247 (ε, 28,800), 277 (ε, 8,100), shoulder 307 mμ (ε, 1,800); infrared cm^{-1}, 3500~3300 broad(s), 3155 broad(s), 1630(s), 1575(s), 1530(m), 1470(w), 1420(s), 1360(w), 1250(m), 1213(s), 1140(m), 1017(w), 971(s), 918(w), 835~820 broad(w), 805(w), 700(w), 640(w), 624(m), 580(m), 524(w).

Anal. Calcd. for $C_4H_4ClN_3O$: C, 33.01; H, 2.77; N, 28.87. Found: C, 32.75; H, 2.85; N, 29.17.

General Preparation of 4-Amino-3-cyanopyridazines.

A mixture of 0.01 mole of the appropriate 5-aminopyridazine 1-oxide and 0.011 mole of dimethylsulfate was heated on a steam bath for 4 hours. After cooling, the product was dissolved in a mixture of 15 ml. of dioxane and 7 ml. of water. To the resulting solution was added dropwise a solution of one g. (0.0154 mole) of potassium cyanide in 4 ml. of water while stirring and maintaining a temperature of 0-5° during the addition. The mixture was stirred for an additional half-hour at room temperature and cooled. The solid that separated was collected, washed with water and dried. The crude 4-amino-3-cyanopyridazine was purified by recrystallization from methanol.

In the case of 4-amino-3-cyanopyridazine which was found to be soluble in water and unstable in the reaction medium, 20 ml. of water was used as the reaction solvent (in the second step of the reaction) for 0.04 mole of 5-aminopyridazine 1-oxide. The 4-amino-3-cyanopyridazine was collected by filtration after the reaction mixture was stirred for 10 minutes at 0-10°.

4-Amino-5,6-dichloro-3-cyanopyridazine (**30**).

The compound was obtained in 69% yield, m.p. 267.5-268.5°. In a larger scale preparation, the ratio of dimethylsulfate should be increased. Thus, in an experiment using 5.4 g. (0.03 mole) of the *N*-oxide (**24**), 8.4 g. (0.067 mole) of dimethylsulfate was employed. Recrystallization of the crude product (5.6 g.) from methanol gave

4.1 g. (72%) of the pure 4-amino-3-cyano-5,6-dichloropyridazine (**30**), fine yellow needles, m.p. 267-268°; U. V. λ max (95% ethanol), 224 (ε, 24,200), 265 (ε, 6,200), 324 mμ (ε, 4,100); infrared cm^{-1}, 3340(s), 3310(s), 3175(s), 2705(w), 2235(w), 1645(s), 1550(s), 1495(w), 1460(w), 1355(m), 1253(m), 1156(m), 1090(w), 980(m), 851(w), 642(m), 613(w), 552(w), 479(w).

Anal. Calcd. for $C_5H_2Cl_2N_4$: C, 31.77; H, 1.07; N, 29.65. Found: C, 32.02; H, 1.19; N, 29.52.

4-Amino-5-chloro-3-cyano-6-methoxypyridazine (**32**).

This compound was obtained in 87% yield as colorless needles, m.p. 235-236°; U. V. λ max (95% ethanol), 216 (ε, 29,300), 312 mμ (ε, 3,100); infrared cm^{-1}m 3410(s), 3330(s), 3230(m), 3000(w), 2950(w), 2850(w), 2225(w), 1650(s), 1630(m), 1575(s), 1505(s), 1485(m), 1460(w), 1450(m), 1370(s), 1300(m), 1218(m), 1193(m), 1140(w), 1086(m), 965(m), 844(w), 763(w), 735(w), 678(w), 654(w), 560(w), 510(m), 493(m), 480(m), 420(w).

Anal. Calcd. for $C_6H_5ClN_4O$: C, 39.04; H, 2.73; N, 30.35. Found: C, 39.41; H, 2.84; N, 29.96.

4-Amino-3-cyano-6-methoxypyridazine (**29**).

This compound was obtained as colorless leaflets, m.p. 257-258° dec., 85% yield; U. V. λ max (95% ethanol), 218 (ε, 29,500), shoulder 226 (ε, 23,500), shoulder 249 (ε, 3,800), 310 mμ (ε, 3,100); infrared cm^{-1}, 3395(s), 3335(m), 3135 broad(s), 3050(m), 2955(w), 2860(w), 2745(w), 2230(w), 1310(s), 1239(s), 1195(m), 1090(w), 990(w), 967(w), 875(m), 764(w), 710(w), 694(w), 586(w), 542 broad(m), 500(w), 470(w).

Anal. Calcd. for $C_6H_6N_4O$: C, 48.00; H, 4.03; N, 37.32. Found: C, 47.90; H, 3.97; N, 37.29.

4-Amino-3-cyano-6-chloropyridazine (**31**).

This compound was obtained in 25% yield as colorless needles from acetone-water, m.p. 273° dec.; U. V. λ max (95% ethanol), 213 (ε, 22,800), 228 (ε, 16,500), 260 (ε, 8,600), 320 mμ (ε, 3,100); infrared cm^{-1}, 3385(s), 3100 broad(s), 3050(s), 2705(w), 2240(w), 1670(s), 1645(m), 1575(s), 1510(w), 1480(w), 1465(w), 1410(w), 1380(m), 1280(m), 1204(m), 1176(m), 1094(m), 1062(m), 1011(w), 981(s), 893(s), 748(m), 720 broad(w), 668(w), 647(w), 580 broad(m), 508(w), 450(w), 415(w).

Anal. Calcd. for $C_5H_3ClN_4$: C, 38.85; H, 1.96; N, 36.25. Found: C, 39.04; H, 2.14; N, 36.04.

4-Amino-3-cyanopyridazine (**16**).

This compound was obtained in 46% yield as colorless needles from ethyl acetate, m.p. 222°; U. V. λ max (95% ethanol), 214 (ε, 12,400), 254 (ε, 11,500), 317 mμ (ε, 3,200); infrared cm^{-1}, 3360(s), 3125 broad(s), 3050(s), 2725(w), 2700(w), 2230(m), 1680(s), 1640(m), 1575(s), 1480(m), 1380(m), 1325(w), 1196(m), 1162(s), 1043(s), 906(m), 855(m), 764(w), 758(w), 743(m), 695(w), 607(m), 585(s), 475(w).

Anal. Calcd. for $C_5H_4N_4$: C, 50.00; H, 3.36; N, 46.64. Found: C, 50.23; H, 3.71; N, 46.60.

4-Amino-5,6-dichloropyridazine-3-carboxamide (**35**).

To 35 ml. of concentrated sulfuric acid was added 5 g. (0.0265 mole) of 4-amino-3-cyano-5,6-dichloropyridazine (**30**) and heated at 80-85° for one hour. The mixture was poured into ice water and was made alkaline with aqueous ammonia. The precipitate was filtered, washed with water and dried, weighing 5.4 g. The product was recrystallized from methanol, giving 4.3 g. of colorless leaflets, m.p. 273-274° and 0.7 g. of a second crop of the same melting points, total yield, 5.0 g. (92%); U. V. λ max (95% ethanol), 218 (ε, 22,300), 264 (ε, 6,500), 322 mμ (ε, 3,900); infrared cm^{-1}, 3475(s), 3390(m), 3275(m), 3175(m), 1675(s), 1520(s), 1510(w), 1460(m), 1410(m), 1360(m), 1241(s), 1171(m), 1138(s), 1095(w), 982(s), 838(m), 802(m), 751(w), 712(s), 630(m), 589(m), 533(w), 510(m), 431(m).

Anal. Calcd. for $C_5H_3Cl_2N_4O$: C, 29.15; H, 1.47; N, 27.19. Found: C, 29.46; H, 1.77; N, 27.44.

4-Aminopyridazine-3-carboxamide (**36**).

A mixture of 5 g. (0.024 mole) of 4-amino-5,6-dichloropyridazine-3-carboxamide (**35**), 10 ml. of 28% aqueous ammonia, 0.5 g. of 5% palladium-charcoal and 40 ml. of methanol was hydrogenated at atmospheric pressure. The reduction stopped when the calculated amount of hydrogen had been absorbed. After removal of the catalyst by filtration the filtrate was evaporated to dryness, the residue was washed with acetone and filtered. Evaporation of the acetone from the filtrate and recrystallization from ethanol gave 3.2 g. (98%) of 4-aminopyridazine-3-carboxamide as colorless plates, m.p. 187-188°; U. V. λ max (95% ethanol), 256 (ε, 13,100), 315 mμ (ε, 3,900); infrared cm^{-1}, 3440 broad(s), 3330 broad(s), 3220 broad(s), 1700(s), 1675(s), 1620(s), 1545(w), 1475(w), 1415(m), 1380(w), 1340(w), 1325(w), 1212(s), 1196(s), 1147(w), 1090(m), 1070(w), 1050(w), 898(m), 846(w), 808(w), 746(w), 668(m), 583(m), 557(m), 530(m), 508(m).

Anal. Calcd. for $C_5H_6N_4O$: C, 43.48; H, 4.38; N, 40.56. Found: C, 43.66; H, 4.25; N, 40.33.

4-Aminopyridazine-3-carboxylic Acid (**15**) From 4-Aminopyridazine-3-carboxamide (**36**).

A mixture containing 0.4 g. (0.0029 mole) of 4-aminopyridazine-3-carboxamide (**36**) and 4 ml. of 5% aqueous sodium hydroxide solution was heated at 80-85° for 20 minutes. After cooling, the solution was acidified with concentrated hydrochloric acid to *p*H 2 and the crystalline material which separated was removed by filtration. Recrystallization from water afforded 0.35 g. (87%) of colorless needles, m.p. 222° dec.; U. V. λ max (water), 271 (ε, 2,900), 290 mμ (ε, 1,300); infrared cm^{-1}, 3290(m), 3060(m), 2720(w), 2060(w), 1990(m), 1625(s), 1570(m), 1500(w), 1450(w), 1400(m), 1330(m), 1264(w), 1243(m), 1165(m), 1139(w), 1055(m), 975(w), 905(w), 893(w), 873(w), 859(m), 821(s), 809(w), 718(w), 675(s), 568(s), 540(w), 441(w), 410(w).

Anal. Calcd. for $C_5H_5N_3O_2$: C, 43.18; H, 3.62; N, 30.21. Found: C, 43.38; H, 3.62; N, 30.04.

4-Aminopyridazine-3-carboxylic Acid (**15**) from 4-Amino-3-cyanopyridazine (**16**).

A solution containing 2.6 g. (0.03 mole) of 4-amino-3-cyanopyridazine (**16**) and 50 ml. of 10% aqueous sodium hydroxide was heated on the steam bath for one hour. After cooling, the solution was acidified with dilute hydrochloric acid to *p*H 2. The solid precipitate was removed by filtration and recrystallized from water, yield 2.4 g. (88%), m.p. 222° dec. The ultraviolet and infrared spectra were identical with those described above.

4-Amino-6-methoxypyridazine-3-carboxylic Acid (**34**).

A mixture containing 2.5 g. (0.017 mole) of 4-amino-3-cyano-6-methoxypyridazine (**29**) and 50 ml. of 5% aqueous sodium hydroxide solution was heated at 80-85° on a steam bath until the crystals went into solution. The solution was adjusted to *p*H 3.5 by the addition of concentrated hydrochloric acid and allowed to stand in the refrigerator. The crystalline precipitate was collected by filtration and washed with a small quantity of cold water to give the pure carboxylic acid, m.p. 187-188° dec., yield, 2.65 g. (94%). An analytical sample was prepared by recrystallization from water, colorless prisms, m.p. 188° dec.; U. V. λ max (95% ethanol), 218 (ε, 22,400), 225 (ε, 20,700), shoulder 250 (ε, 3,600),

303 mμ (ε, 2,700); infrared cm^{-1}, 3430 broad(m), 3300(m), 3130(w), 3050(m), 2900(m), 2745(w), 2300 broad, 1645(s), 1620(s), 1590(s), 1515(w), 1490(w), 1450(m), 1400(w), 1330(s), 1265(s), 1222(m), 1210(w), 1157(w), 1105(w), 1037(w), 998(m), 948(w), 882(m), 808(m), 758(m), 670(m), 625(m), 597(w), 536(w), 500(w).

Anal. Calcd. for $C_6H_7N_3O_3$: C, 42.61; H, 4.17; N, 24.84. Found: C, 42.66; H, 4.33; N, 24.79.

Pyrimido[5,4-c]pyridazine-6,8-dione (**37**).

To one g. (0.0165 mole) of molten urea heated at 150° was added 0.5 g. (0.0036 mole) of 4-aminopyridazine-3-carboxamide and the temperature was raised to 200° over a period of 15 minutes. The mixture was kept at 200-210° for an additional 50 minutes, whereupon, crystallization occurred. The product was diluted with water, acidified with hydrochloric acid to *p*H 4-6 and the insoluble material collected by filtration. This was dissolved in dilute aqueous sodium hydroxide solution and the filtered solution made acidic with acetic acid. The crystals that separated were collected after cooling and recrystallized repeatedly from water to yield hydrated pyrimido[5,4-c]pyridazine-6,8-dione as colorless plates, yield, 0.2 g. (30%), m.p. shrinking and darkening at 380° and not completely melted at 400°.

Anal. Calcd. for $C_6H_4N_4O_2 \cdot H_2O$: C, 39.57; H, 3.32; N, 30.76. Found: C, 39.65; H, 3.26; N, 30.66.

An anhydrous sample was obtained after drying at 100° for 2 days *in vacuo;* U. V. λ max (95% ethanol), 208 (ε, 21,400), 250 (ε, 7,900), 295 mμ (ε, 3,200); infrared cm^{-1}, 3210 broad (s), 3160 broad(s), 3080 broad(s), 3000 broad(s), 2850(m), 2800(m), ~2300 broad, 1715(s), 1625(m), 1600(s), 1450(m), 1420(s), 1335(s), 1300(s), 1280(m), 1180(w), 1154(m), 1117(w), 1055(m), 992(w), 931(w), 867(w), 808(w), 782(s), 696(m), 646(w), 575(w), 554(w), 490(m), 453(m).

Anal. Calcd. for $C_6H_4N_4O_2$: C, 43.91; H, 2.46; N, 4.14. Found: C, 43.69; H, 2.63; N, 34.00.

Pyrimido[5,4-c]pyridazin-8-one (**38**).

A mixture of 0.2 g. (0.00145 mole) of 4-aminopyridazine-3-carboxamide and 10 ml. of ethyl orthoformate was heated under reflux for 6 hours, during which time the crystalline pyrimido-[5,4-c]pyridazin-8-one separated from solution. Cooling the reaction mixture in the refrigerator overnight, dilution with ether, filtration and washing with ether gave 0.2 g. (91%) of crystalline solid, m.p. >300°. Crystallization from methanol formed colorless needles, m.p. >300°; U. V. λ max (95% ethanol), 230 (ε, 10,600), 285 mμ (ε, 7,100); infrared cm^{-1}, 3180(m), 3060 broad(s), 3000(m), 2925(m), 2885(m), 1705(s), 1610(s), 1575(s), 1530(m), 1475(m), 1435(m), 1380(m), 1360(s), 1290(s), 1170(m), 1102(m), 1041(w), 923(m), 863(m), 841(s), 822(m), 740(w), 607(m), 540(m), 497(w), 465(m).

Anal. Calcd. for $C_6H_4N_4O$: C, 48.65; H, 2.72; N, 37.82. Found: C, 48.77; H, 2.72; N, 37.81.

Crystallization from water gave hydrated material, colorless needles, m.p. 316° dec.

Anal. Calcd. for $C_6H_4N_4O \cdot H_2O$: C, 43.38; H, 3.64. Found: C, 43.64; H, 3.73.

Pyrimido[5,4-c]pyridazine-8-thione (**39**).

A slurry containing 0.3 g. (0.002 mole of pyrimido[5,4-c]-pyridazin-8-one and 20 ml. of anhydrous pyridine was stirred and refluxed and to this refluxing mixture was added portionwise 1.1 g. (0.005 mole) of finely pulverized phosphorus pentasulfide. Upon addition of the first amount of phosphorus pentasulfide the reaction mixture turned deep purple. The solution was stirred and refluxed for one hour, then the excess pyridine was removed under reduced pressure. The pasty residue was diluted with 50 ml. of water and the mixture was heated on the steam bath for one hour, then filtered while hot. The black solid was dissolved in 5% sodium hydroxide solution, the solution was heated on the steam bath for 30 minutes, filtered and the filtrate acidified by the addition of concentrated hydrochloric acid to *p*H 4. The precipitate was collected by filtration and washed with water. This procedure was repeated 3 times and the dark grey powder was dried at 100° *in vacuo,* m.p. >400°, yield 0.1 g. (30%); U. V. λ max (0.1 *N* sodium hydroxide), 246 (ε, 8,000), 332 (ε, 2,800), 428 mμ (ε, 7,400); infrared cm^{-1}, 3070 broad(m), 2880 broad(m), ~2500 broad, 1705(m), 1595(s), 1550(s), 1490(s), 1415(m), 1375(m), 1315(m), 1290(m), 1240(w), 1203(s), 1142(m), 1105(w), 1050(w), 922(w), 868(w), 841(m), 824(w), 810(w), 718(w), 625(w), 598(w), 560(w), 520(m), 470(m).

Anal. Calcd. for $C_6H_4N_4S$: C, 43.91; H, 2.46; N, 34.14. Found: C, 44.20; H, 2.20; N, 34.11.

The Hydrolytic Ring-opening of Pyrimido[5,4-c]pyridazin-8-one (**38**).

A solution containing 0.5 g. (0.34 mmole) of pyrimido[5,4-c]-pyridazin-8-one (**38**) and 0.6 ml. of deuterium oxide containing a small amount of sodium deuteroxide was allowed to stand at room temperature for one week. During this period the NMR spectrum was recorded periodically. The peaks at 9.15 δ (doublet), 8.34 δ (singlet) and 7.61 δ (doublet) (ring protons) gradually diminished and new peaks (ring protons at 8.47 δ (doublet) and 6.87 δ (doublet) appeared. After one week, the solution was acidified by addition of concentrated hydrochloric acid to *p*H 2-2.5. The crystalline solid which separated was removed by filtration, washed with water and dried, m.p. 222° dec., undepressed on admixture with an authentic sample of 4-aminopyridazine-3-carboxylic acid (**15**). The infrared spectra of the two samples were identical.

8-Aminopyrimido[5,4-c]pyridazine (**41**).

A solution containing 0.7 g. (0.0058 mole) of 4-amino-3-cyanopyridazine (**16**) and 6 ml. of formamide was heated under reflux for 2 hours. After cooling, the crystalline solid was collected by filtration and purified by sublimation *in vacuo*, yield 0.3 g. (35%), m.p. 295° dec.; U. V. λ max (95% ethanol), 206 (ε, 16,900), 217 (ε, 10,300), 242 (ε, 10,600), 329 mμ (ε, 6,100); infrared cm^{-1}, 3320(m), 3150(w), 2650(w), 1675(s), 1640(s), 1580(s), 1570(s), 1500(s), 1460(m), 1380(m), 1330(s), 1235(s), 1181(w), 1150(m), 1120(w), 1005(s), 933(s), 854(s), 740(m), 700(m), 640(s), 603(m), 536(s), 515(w), 500(w), 470(s).

Anal. Calcd. for $C_6H_5N_5$: C, 48.98; H, 3.42; N, 47.59. Found: C, 48.69; H, 3.72; N, 47.26.

Acknowledgment.

This investigation was supported by PHS Grant No. Ca-04327-08 and -09 from the National Cancer Institute, Public Health Service. The authors are grateful to Mrs. Shigeko Nakagome and to Mrs. Ruby Ju for the analytical data and for the ultraviolet spectra. The authors wish to thank Dr. William M. Litchman for valuable discussions concerning the nmr spectra.

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Received April 25, 1968 Albuquerque, New Mexico 87106