procedure from 3-amino-6-chloropyridazine in 76% yield: mp 154–155° (ethanol); uv (ethanol) λ_{max} 254 and 340 nm (ϵ 11,000 and 8850); nmr ($CDCl_3$) τ 1.04 (s, H_2), 2.38 (d, H_8), 2.02 (d, H_9) ($J_{8,9}$ = 9.2), 5.56 (q, CH_2), 8.58 (t, CH_3) (J = 6.6).

Anal. Calcd for $C_{10}H_8ClN_3O_3$: C, 47.35; H, 3.17; N, 16.57. Found: C, 47.39; H, 3.09; H, 3.09; N, 16.80.

3-Carbethoxy-4-hydroxy-4-methoxypyrimido[1,2-*b*]pyridazine (IX).—Compound VIII (R = H; 0.5 g), methanol (10 ml), and few drops of concentrated hydrochloric acid were heated under reflux for 3 hr. Upon evaporation *in vacuo* to half of the original volume and after standing on ice overnight, the separated product (0.35 g) had mp 158–160° (at 150° on a preheated melting point apparatus); ir (Nujol) 2247 (hydrogen bonded OH) and 1754 cm^{-1} (CO). From the melt a new compound separated and had mp 168–170° (identical with the starting pyrimidopyridazinone): nmr of IX ($CDCl_3$) τ 0.95 (s, H_2), 6.00 (s, OCH_3), 1.14 (dd, H_7), 2.28 (dd, H_8), 1.95 (dd, H_9) ($J_{7,8}$ = 5.5, $J_{8,9}$ = 8.5, $J_{7,9}$ = 2.5), 5.55 (q, CH_2), 8.58 (t, CH_3).

From the nmr spectrum it is evident that the adduct is in equilibrium with the starting compound (ratio of about 1:1). When heated *in vacuo* the adduct is reconverted to the starting bicyclic compound.

2,9-Dimethylpyrido[1,2-*a*]pyrimidin-4-one (II, R_1 = H; R = R_2 = CH_3).—The procedure for the synthesis of IV was followed, but using 2-amino-3-methylpyridine and acetoacetic ester (yield 71%), mp 131–132° (from *n*-hexane and ethyl acetate) (lit.[3] mp 131–132°).

Anal. Calcd for $C_{10}H_{10}N_2O$: C, 68.95; H, 5.79; N, 16.08. Found: C, 69.17; H, 5.98; N, 16.08.

2,8-Dimethylpyrido[1,2-*a*]pyrimidin-4-one (II, R_2 = H; R = R_1 = CH_3).—The compound was prepared as the above analog from 2-amino-4-methylpyridine in 74% yield, mp 136–137° (from *n*-hexane and ethyl acetate).

Anal. Calcd for $C_{10}H_{10}N_2O$: C, 68.95; H, 5.79; N, 16.08. Found: C, 68.64; H, 5.57; N, 16.20.

Registry No.—III (R_1 = CH_3), 30247-66-6; III (R_1 = C_6H_5), 30247-67-7; IV (R = R_2 = H; R_1 = $COOC_2H_5$), 30247-68-8; IV (R = R_2 = H; R_1 = COOH), 30247-69-9; V, 30247-70-2; VIII (R = H), 19111-57-2; VIII (R = Cl), 30247-72-4; IX, 30247-73-5; cyclopentan-2-onecarboxylic acid 3-pyridazinyl amide, 30318-65-1; 7-chloro-2,4-dimethylpyrido[3,2-*d*]-pyrimido[1,2-*b*]pyridazin-5-ium perchlorate, 30247-74-6; pyrido[1,2-*a*]pyrimidin-5-ium perchlorate, 30247-75-7; 2,4-dimethylpyrido[1,2-*a*]pyrimidin-5-ium perchlorate, 30247-60-0.

Reaction of 4,6-Dimethoxy-5-nitropyrimidine with Methylhydrazine. Formation of 4-Hydrazino-6-hydroxypyrimidine

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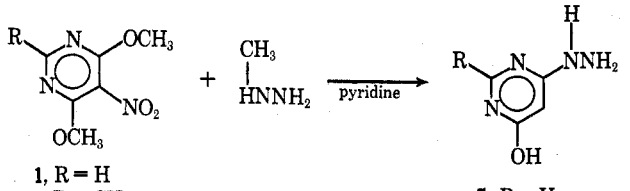
The reaction of 4,6-dimethoxy-5-nitropyrimidine (1) with methylhydrazine in refluxing pyridine or butanol is very complex involving the methylation of the solvent by 1 and the nucleophilic substitution and demethylation of the methylhydrazino substituent in the 5 position to yield 4-hydrazino-6-hydroxypyrimidine. The first step in this sequence of reactions involves the methylation of the solvent, followed by nucleophilic substitution of methylhydrazine in the 4 position, migration of its methyl substituent to form a carbon to oxygen bond with the adjacent nitro substituent, and eventual elimination of methyl nitrite from the 5 position as one of the reaction products. 4,6-Dimethoxy-5-nitropyrimidine reacts with pyridine (in the absence of methylhydrazine) to yield an insoluble methylpyridium salt which is not a precursor of 4-hydrazino-6-hydroxypyrimidine. The mother liquor from this reaction on acid hydrolysis yields 4-hydroxy-6-methoxy-5-nitropyrimidine and reacts with methylhydrazine to yield 4-hydroxy-6-hydrazinopyrimidine. Both 4-chloro-6-hydroxy-5-nitropyrimidine and 4,6-dichloro-5-nitropyrimidine react with methylhydrazine in ethanol to yield the corresponding methylhydrazino derivatives.

In previous work,[1] the reaction of methylhydrazine with 4,6-dimethoxy-5-nitropyrimidine (**1**) in an alcoholic solvent was found to be unexpectedly complex. We have continued the investigations of the reactions of **1** and the 2-methyl and 2-phenyl analogs (**2** and **3**) and 4,6-diethoxy-5-nitropyrimidine (**4**) and have established that the products are the 4-hydrazino-6-hydroxypyrimidines **5**–**7**.

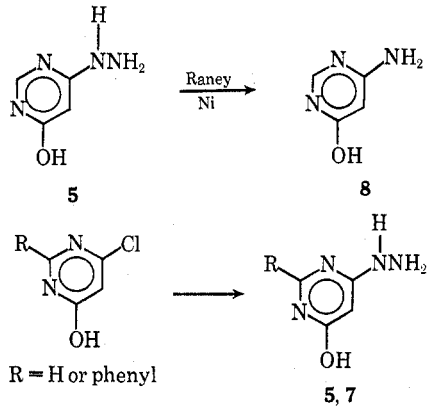


1, R = H
2, R = CH_3
3, R = C_6H_5

5, R = H
6, R = CH_3
7, R = C_6H_5

The structures were initially inferred from the spectral data which showed the probable presence of either a hydrazino, amino, or hydroxyl substituent and the absence of the methoxy and nitro substituents of the original starting material **1**. High-resolution mass spectral measurements gave apparent molecular formulas $RC_4H_5N_4O$, R = H or phenyl.

The hydrazino structures were finally established by hydrogenolysis of **5** to give 4-amino-6-hydroxypyrimidine[2] (**8**) and by the synthesis of **5** and **7** from the reac-



5

8

5, 7

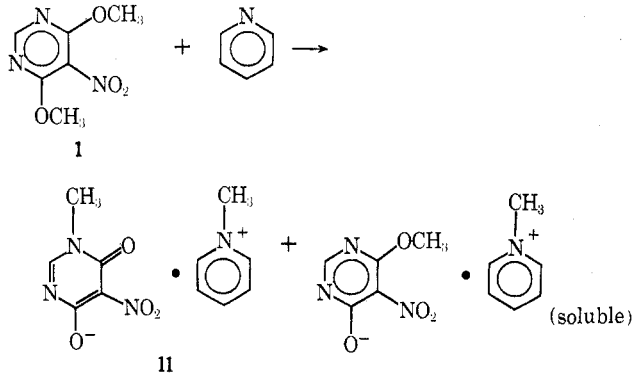
(1) M. H. Krackov and B. E. Christensen, *J. Org. Chem.*, **28**, 2677 (1963).

(2) D. J. Brown, *J. Soc. Chem. Ind., London*, **69**, 353 (1950).

tions of the respective 6-chloropyrimidines[3,4] with hydrazine.

In an effort to ascertain the mechanism of this unusual reaction, 4,6-di(1-methylhydrazino)-5-nitropyrimidine (**9**), 4-methoxy-6-(1-methylhydrazino)-5-nitropyrimidine (**10**), and 5-amino-4,6-dimethoxypyrimidine were synthesized and subjected to the same reaction conditions with methylhydrazine in refluxing pyridine as **1**. No evidence for the formation of **5** was observed in these experiments, indicating that these compounds could not have served as an intermediate in the course of this reaction.

Since neither **9** or **10** was a precursor of **5**, the behavior of **1** in refluxing pyridine was investigated to determine if the initial step involved a reaction with the solvent. This reaction gave an insoluble crystalline salt in 25% yield which was shown to be the methylpyridinium salt of 1,6-dihydro-4-hydroxy-1-methyl-5-nitro-6-oxopyrimidine (**11**).

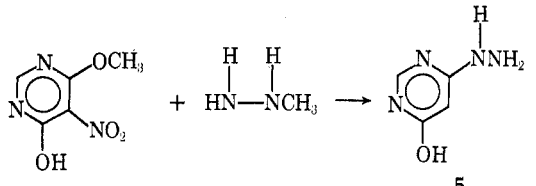


11

The nmr spectrum of **11** showed that the two equivalent methoxyl groups of **1** absorbing at δ 4.12 ($DCCl_3$) had split into two 3-proton singlets absorbing at δ 3.42 and 4.42 (D_2O), corresponding to those of the *N*-methyl groups in *N*-methylpyridinium iodide (δ 4.46) and 1,3-dimethyluracil (δ 3.30 and 3.43[5]). These changes were accompanied by the disappearance of the strong absorption band in the 1125-cm^{-1} region of the ir spectrum which is attributed to the methoxyl groups of **1** and the appearance of an absorption band at about 1650 cm^{-1}, indicative[6] of a conjugated amide carbonyl group in **11**. Hydrolysis of **11** gave 1,6-dihydro-4-hydroxy-1-methyl-5-nitro-6-oxopyrimidine (**12**) [δ 9.07 (1 H) and 3.62 (3 H)].

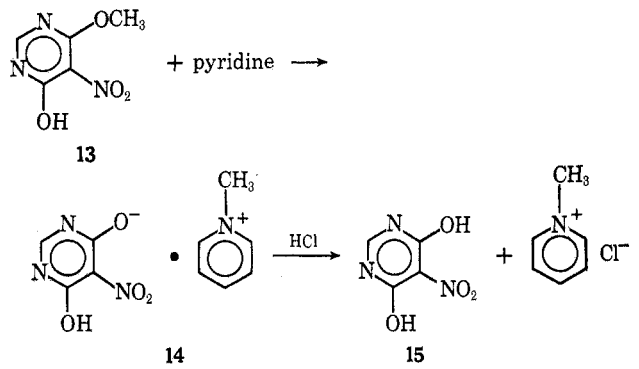
As expected, **11** was not a precursor of 4-hydrazino-6-hydroxypyrimidine but the mother liquor from the crystallization of **11**, when treated with methylhydrazine, did yield **5** in substantial amounts. After removal of pyridine, 4-hydroxy-6-methoxy-5-nitropyrimidine[7] (**13**) was isolated from the acidified residue in approximately 30% yield.

The isolation of **13** suggested that the first reaction in the sequence leading to **5** involved the methylation of pyridine followed by reaction of the methyl pyridinium salt of **13** with methylhydrazine. The compound **13** was synthesized[7] and treated with methylhydrazine in refluxing pyridine; this gave **5** in an 87% yield as contrasted to 65% in the original reaction.



13 5

The demethylation reaction observed with **1** in refluxing pyridine also occurred with the monomethoxy compound **13**. The resulting methylpyridinium salt obtained in 65% yield gave 5-nitro-4,6-dihydroxypyrimidine (**15**) in 86% yield. The mother liquor from the experiments yielding **14** gave **5** in much smaller yield when treated with methylhydrazine. This confirmed the presence of some unreacted **13** in the mother liquor.



13 14 15

The volatile products from the reaction which yielded **5** were isolated and investigated. The alkalinity of volatile vapors which were not removed by a cold water condensor was substantial, indicating the presence of ammonia or methylamine. Examination of the volatile products after trapping out the amines revealed the presence of methyl nitrite and another compound which may have been cyanic acid. Gas–liquid chromatography detected methanol in the mother liquor.

The first step in the sequence of reactions leading to **5** must therefore involve the methylation of the solvent by **1**. A plausible sequence of reactions that will account for the loss of the nitro substituent by **1** are shown in Scheme I.

Additional support for this mechanism stems from the following considerations: (1) the failure of 4-chloro-6-hydroxy-5-nitropyrimidine to behave in the same manner as 4-hydroxy-6-methoxy-5-nitropyrimidine in the presence of methylhydrazine and ethanol; (2) the work of Kauffmann[8] which predicts the presence of hydrazide ions in basic solution of hydrazine which are essential for this mechanism to proceed.

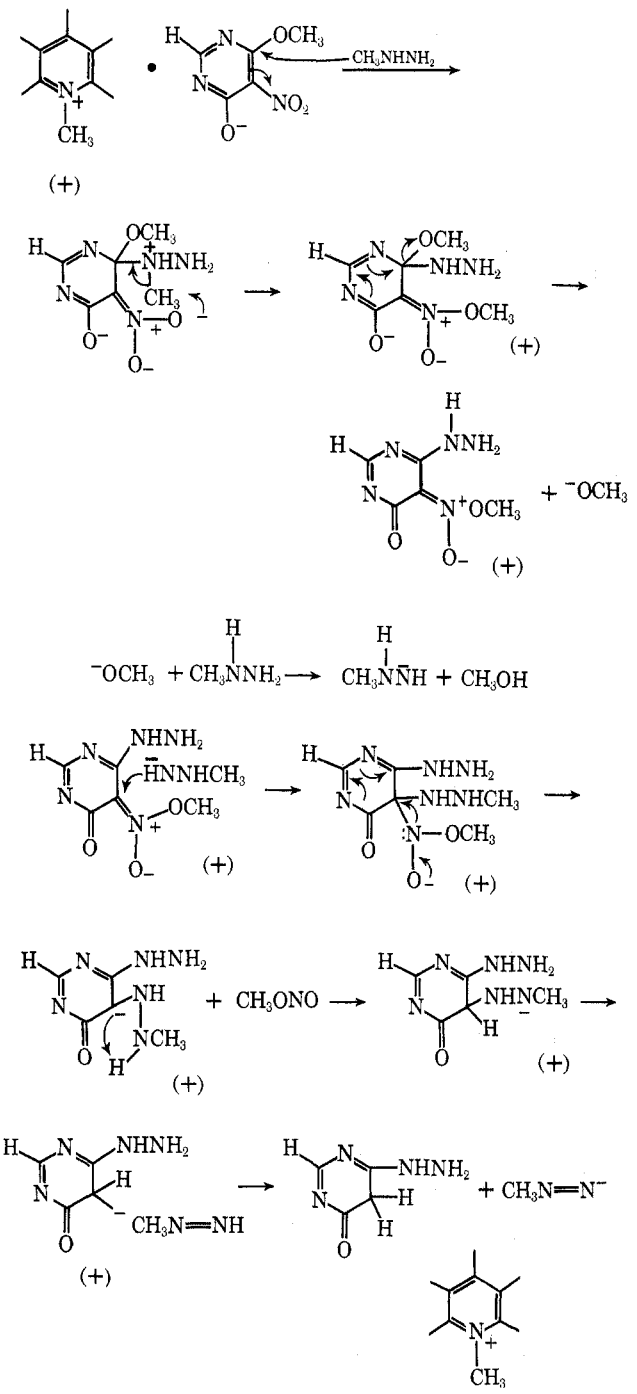
Experimental Section

All melting points were taken on a Fisher-Johns melting point apparatus and are uncorrected. The infrared spectra with the exception of the methyl nitrite spectra were obtained with a Beckman Model IR-8 spectrophotometer with the samples in the form of potassium bromide pellets. The methyl nitrite spectra were obtained through the use of a Beckman Model IR-7

(3) J. A. Hendry and R. F. Homer, *J. Chem. Soc.*, 328 (1952).
(4) D. J. Brown and J. S. Harper, *ibid.*, 1298 (1961).
(5) Varian Associates, "High Resolution NMR Spectra Catalog," Vol. 2, 1963.
(6) K. Nakanishi, "Infrared Absorption Spectroscopy," Holden-Day, San Francisco, Calif., 1962, p 233.
(7) G. M. Kheijets and N. V. Khromov-Borisov, *J. Org. Chem. USSR*, **2**, 1492 (1966).
(8) T. H. Kauffmann, *Angew. Chem., Int. Ed. Engl.*, **3**, 342 (1964); T. H. Kauffman, *et al.*, *Angew. Chem.*, **79**, 918 (1960).

SCHEME I

1 + pyridine ⟶ methylpyridinium salt of **13**



spectrophotometer using a gas cell with sodium chloride windows. The nuclear magnetic resonance spectra were recorded on a Varian A-60 spectrometer. An external standard of 10% tetramethylsilane in deuteriochloroform was used for the samples run in deuterium oxide solutions. The carbon–hydrogen analyses were obtained through the use of a Coleman Model 33 carbon–hydrogen analyzer. A Coleman Model 29 nitrogen analyzer was used to obtain the nitrogen analyses. Mass spectra were determined with a Varian M-66 mass spectrometer and an AEI MS-9 (high-resolution spectra) with a 200° probe temperature and 70-eV energy.

4,6-Dimethoxy-2-methyl-5-nitropyrimidine (2).—To a rapidly stirred solution of sodium methoxide [prepared by adding 4.8 g (0.21 g-atom) of sodium to 150 ml of reagent grade methanol] was added dropwise over a period of 30 min 100 ml of a methanolic solution containing 11.0 g (0.053 mol) of 4,6-dichloro-2-methyl-5-nitropyrimidine. The pale red mixture was allowed to reflux for 1 hr and then the methanol was removed by distillation leaving a thick paste. An ice–water slurry (approximately 400 ml) was added and the mixture brought to neutrality (litmus) with 6 *N* hydrochloric acid. The precipitate was collected, washed well with cold water, and dried to yield 10.2 g (97%) of the cream-colored product, mp 123–124° (Urban and Schnider[9] reported an 86% yield, mp 116–117°). A small amount was recrystallized from methanol, mp 124.0–124.5°.

4,6-Dimethoxy-5-nitro-2-phenylpyrimidine (3).—Finely powdered 4,6-dichloro-5-nitro-2-phenylpyrimidine[10] (40.5 g, 0.15 mol) was suspended in 200 ml of anhydrous methanol and the mixture then cooled in an ice bath. A solution of sodium methoxide, prepared by adding 13.8 g (0.60 g-atom) of sodium to 300 ml of anhydrous methanol, was introduced dropwise into the stirred suspension at a rate which did not allow the temperature to rise above 20°. After the addition was complete, the mixture was refluxed for 1 hr, whereupon on cooling it was poured with vigorous stirring into 400 ml of ice-cold water. The precipitate was collected, washed well with cold water, and dried to yield 36.9 g (94.4%) of a yellow material. Recrystallization from ligroin (bp 90–120°) gave pale yellow needles: mp 122.5–123°; nmr (TFA) δ 7.77 (m, 2), 7.04 (m, 3), 3.75 ppm (s, 1).

Anal. Calcd for $C_{12}H_{11}N_3O_4$: C, 55.2; H, 4.2; N, 16.1. Found: C, 55.3; H, 4.2; N, 15.8.

4,6-Diethoxy-5-nitropyrimidine (4).—A solution consisting of sodium ethoxide [4.6 g of sodium (0.2 g-atom) in 100 ml of ethanol] was added to 19.4 g (0.1 mol) of 4,6-dichloro-5-nitropyrimidine in 160 ml of absolute ethanol. The sodium ethoxide solution was added slowly so as to keep the temperature between 28–32°. After addition of the sodium ethoxide, the mixture was stirred 2 hr and then poured over ice. The precipitate was filtered, dried, and recrystallized from petroleum ether to yield needles (15.5 g, 73%), mp 62–63°.

Anal. Calcd for $C_8H_{11}N_3O_4$: C, 45.1; H, 5.2. Found: C, 45.0; H, 5.3.

4-Hydrazino-6-hydroxypyrimidine (5). A.—Into a refluxing solution containing 1.85 g (0.01 mol) of 4,6-dimethoxy-5-nitropyrimidine in 50 ml of reagent grade pyridine was pipetted 1.84 ml of methylhydrazine causing an immediate yellow coloration; the solution was allowed to reflux for 1 hr. During the first 5 min of the reflux period, a fine white material began to precipitate. After cooling in the refrigerator, the solution was filtered and the product filter cake washed with cold methanol to yield 0.71–0.82 g (56–65%) of crude cream-colored product, mp 245–255° dec. Evaporation of the filtrate yielded only unidentified products which exhibited mainly end absorption in its ultraviolet spectra. Recrystallization of the solid product twice from an ethanol–water solvent (1:1) produced fine long white crystals which decomposed on heating at 237°: uv max (H_2O pH 1) 212 (21,400), 258 mμ (5040); ir (Nujol) 3320, 3257, 3186 (hydrazino NH), 1667 (cyclic amide CO), 1626 (hydrazino NH_2); nmr (TFA) δ 8.11 (s, 1), 6.06 ppm (s, 1) [on standing peaks shift to 8.3 (s, 1), 5.75 ppm (s, 1)]; mass spectrum 70 eV *m/e* (rel intensity) 126 (100), 110 (40), 99 (43), 96 (17), 83 (9), 69 (28), 68 (60), 41 (19), 40 (28), 28 (41); peaks measured by high-resolution $C_4H_6N_4O$ (126.0547), $C_3H_5N_3O$ (99.0432), $C_4H_4N_2O$ (96.0321), $C_3H_4N_2$ (68.0136).

Anal. Calcd for $C_4H_6N_4O$: C, 38.1; H, 4.8. Found: C, 38.1; H, 4.7.

B.—To a refluxing solution of 2.13 g (0.01 mol) of 4,6-diethoxy-5-nitropyrimidine in 50 ml of pyridine was added 1.84 ml (0.04 mol) of methylhydrazine. The mixture was refluxed for 1 hr, cooled, and filtered. The product was washed with cold methanol and dried. The yield was 0.259 g (20.6%), mp 235–255° dec. The product was shown by infrared spectral analysis to be identical with the product obtained from the similar reaction with 4,6-dimethoxy-5-nitropyrimidine.

C.—Compound **13** (1.71 g, 0.01 mol) in refluxing pyridine was treated with 1.84 ml (0.04 mol) of methylhydrazine. The mixture was refluxed for 30 min, cooled, and filtered. The product was washed with cold methanol and dried. The yield was 1.10 g (87%), mp 235–255° dec. The product was shown by infrared spectral analysis to be identical with the product obtained from the similar reaction with 4,6-dimethoxy-5-nitropyrimidine.

(9) R. Urban and Schneider, *Helv. Chim. Acta*, **41**, 1806 (1958).

(10) H. C. Carrington, F. H. S. Curd, and D. N. Richardson, *J. Chem. Soc.*, 1858 (1955).

Anal. Calcd for $C_4H_6N_4O$: C, 38.1; H, 4.8. Found: C, 38.0; H, 4.7.

D.—To 1.71 g (0.01 mol) of compound **13** in 50 ml of dry benzene was added 1.84 ml (0.04 mol) of methylhydrazine. The mixture was refluxed for 30 min. The product was isolated by filtration, washed with cold methanol, and dried, yield 0.64 g (50.8%), mp 235–255° dec. An infrared spectrum of the compound was identical with that obtained for an authentic sample of 4-hydrazino-6-hydroxypyrimidine.

4-Hydrazino-6-hydroxy-2-methylpyrimidine (**6**).—The procedure was essentially the same as for **5**. Recrystallization twice from ethanol–water (1:2) gave a 51% yield of long white crystals of **6**, mp 155–156° dec. This product also gave a positive blue color test with ferric chloride: uv max (H_2O pH 1) 261 mμ (6810); ir (Nujol) 3335, 3265, 3142 (hydrazino NH), 1671 (cyclic amide CO), 1621 (hydrazino NH_2); nmr (TFA) δ 5.75 (s, 1), 2.17 ppm (s, 3) [on standing peaks shift to δ 5.40 (s, 1), 2.47 (s, 3) ppm]; mass spectrum 70 eV *m/e* (rel intensity) 141 (33), 140 (90), 125 (21), 124 (33), 110 (25), 99 (100), 82 (28), 69 (28), 68 (83), 55 (24), 43 (33), 42 (73), 41 (54), 40 (55), 32 (37), 28 (54).

4-Hydrazino-6-hydroxy-2-phenylpyrimidine (**7**).—The 4,6-dimethoxy-5-nitro-2-phenypyrimidine in hot pyridine did not react with methylhydrazine to give **7** in an isolable yield but instead yielded other products most likely from the cleavage of the pyrimidine ring. By the use of 1-butanol (dried with calcium sulfate and freshly distilled) as solvent, a small amount of **7** was formed.

A solution of 10.4 g consisting of (0.04 mol) of 4,6-dimethoxy-5-nitro-2-phenylpyrimidine and 600 ml of refluxing 1-butanol was added dropwise to a solution of 7.4 ml (0.16 mol) of methylhydrazine in 100 ml of 1-butanol over a period of 45 min. The deep yellow solution was refluxed over 2 hr becoming orange (no precipitation). On cooling in a deep freeze overnight, 2.5 g (31%) of the crude yellow-tan crystals were obtained, mp 210–230° dec. Recrystallization from 1-butanol gave pale yellow crystals: mp 227–228° dec; uv (H_2O pH 1) 206 (34,000), 239 (16,400), 287.5 mμ (8080); ir (Nujol) 3367, 3289, 3252 (hydrazine NH), 1668 (cyclic amide CO), 1618 (hydrazino NH_2), 1568 (aromatic ring); nmr (TFA) δ 7.72 (m, 2), 7.23 (m, 3), 6.02 ppm (s, 1); nmr (DMSO-d_6) 8.39 (m, 3), 7.80 (m, 3), 5.66 (s, 1), 3.65 ppm (s, broad, 2.7); mass spectrum 70 eV *m/e* 202, 187, 186, 173, 172, 160, 159, 144, 124, 104, 99, 75, 74, 69, 56, 43, 42, 32, 31, 28; peaks measured at high resolution $C_{10}H_{10}N_4O$ (202.0851), $C_{10}H_9N_3O$ (187.0746), $C_{10}H_8N_2O$ (172.0641), $C_9H_8N_2$ (144.0689), $C_4H_4N_4O$ (124.0387), C_7H_6N (104.0500), $C_3H_5N_3O$ (99.0433), C_3H_3NO (69.0215). The ir and nmr spectra of the samples were identical with those prepared from authentic compounds.

Anal. Calcd for $C_{10}H_{10}N_4O$: C, 59.5; H, 5.0. Found: C, 59.4; H, 4.8.

4-Amino-6-hydroxypyrimidine (**8**).—The procedure of Ainsworth[11] was modified to prevent the reduction of the pyrimidine ring. To a gently boiling solution of 0.50 g (0.004 mol) of 4-hydrazino-6-hydroxypyrimidine in 10 ml of water and 3 ml of 28% aqueous ammonium hydroxide was added in small portions 2 g of Raney nickel, prepared according to Brown.[2] After completing the addition, the mixture was gently refluxed, with stirring, for 30 min; upon evaporation to dryness 400 mg of crude product was obtained. Recrystallization from water or sublimation yielded 350 mg (79%), mp 264–265°.

Anal. Calcd for $C_4H_5N_3O$: C, 43.2; H, 4.5; N, 37.8. Found: C, 43.1; H, 4.6; N, 37.6.

4-Hydrazino-6-hydroxypyrimidine from 4-Chloro-6-hydroxypyrimidine.—To 2.6 g (0.02 mol) of 4-chloro-6-hydroxypyrimidine[4] dissolved in 100 ml of absolute ethanol heated to approximately 70° was added 1.35 ml (0.04 mol) of 95% anhydrous hydrazine, and the resultant mixture was refluxed for 30 min; within 5 min crystals were observed. Upon cooling, the solution was diluted with 50 ml of water and allowed to stir for an additional 5 min. The precipitate was collected and washed with cold water to yield 1.26 g (50%) of the white product, mp 235–245° dec. Concentration of the mother liquor to about 10 ml gave another 1.0 g (40%) of crude product.

Recrystallization of a small portion from ethanol–water (1:1) solvent gave long white needles which decomposed at *ca.* 237°; its melting point was *ca.* 310° when inserted at 305°.

This compound gives a positive Tollens test, a positive reaction with sodium pentacyanoamineferrate, and (unexpected) positive test (a deep blue color) with ferric chloride solution.

Anal. Calcd for $C_4H_6N_4O$: C, 38.1; H, 4.8. Found: C, 38.1; H, 4.9.

4-Chloro-6-hydroxy-2-phenylpyrimidine.—A mixture of 5 g (0.22 mol) of 4,6-dichloro-2-phenylpyrimidine[3] and 50 ml of 3 *N* sodium hydroxide was refluxed vigorously until only a clear solution remained (approximately 8 hr). The solution cooled in an ice bath was carefully acidified to pH 2–4 with concentrated hydrochloric acid.

After filtering and thoroughly washing with water, the product was pressed and then dried *in vacuo* over phosphorus pentoxide, yield 4.5 g. Recrystallization from isopropyl alcohol yielded fine white needles (92%): mp 226–227°; uv max (H_2O pH 1) 242 (11,500), 289 mμ (9760); nmr (DMSO-d_6) δ 8.17 (m, 2), 7.60 (m, 3), 6.55 (s, 1), 4.20 ppm (s, broad, 1).

Anal. Calcd for $C_{10}H_7ClN_2O$: C, 58.1; H, 3.5; N, 13.6. Found: C, 58.0; H, 3.5; N, 13.3.

4-Hydrazino-6-hydroxy-2-phenylpyrimidine.—The addition of 0.67 ml (0.02 mol) of 95% anhydrous hydrazine to a gently refluxing suspension of 2.1 g (0.01 mol) of 4-chloro-6-hydroxy-2-phenylpyrimidine in 50 ml of absolute ethanol gave a clear colorless solution. This solution was refluxed for 30 min before the product began to precipitate. After refluxing for an additional 30 min, the mixture was cooled and diluted with 25 ml of cold water, and the product was isolated by filtration to yield 1.2 g (59%) of white crystals, mp 239–241° dec. Concentration of the mother liquor to 10 ml gave 0.7 g (35%) more of the crude product. A small portion was recrystallized for analysis from 1-butanol as fine white crystals, mp 239–240° dec.

The product gave a weakly positive test (blue color) with ferric chloride solution. The compound also gave a positive reaction with Tollens reagent and with sodium pentacyanoamineferrate solution.

Anal. Calcd for $C_{10}H_{10}N_4O$: C, 59.5; H, 5.0. Found: C, 59.6; H, 4.9.

4,6-Di(1-methylhydrazino)-5-nitropyrimidine (**9**).—A 250-ml standard taper erlenmeyer flask containing a solution of 1.94 g (0.01 mol) of 4,6-dichloro-5-nitropyrimidine in 200 ml of absolute methanol was cooled to −10°. On addition of 1.85 ml (0.04 mol) of methylhydrazine the solution turned to a yellow color. The solution in the stoppered flask was stirred for 1 hr while allowing the temperature to rise to 20–25°. During this period the product precipitated as a yellow powder. After removing the product by filtration and drying, the yield was 1.85 g (84.5%), mp 175–177° dec. Recrystallization from dioxane gave fine yellow crystals, mp 183.5–184.5° dec.

Anal. Calcd for $C_6H_{11}N_7O_2$: C, 33.8; H, 5.2; N, 46.0. Found: C, 33.9; H, 5.2; N, 45.8.

4-Methoxy-6-(1-methylhydrazino)-5-nitropyrimidine (**10**).—A solution containing 9.48 g (0.05 mol) of 4-chloro-6-methoxy-5-nitropyrimidine[12] in 400 ml of absolute methanol was cooled below 0°. Then 4.6 ml (0.1 mol) of methylhydrazine was pipetted into the solution, producing a yellow color. The solution in a stoppered flask was stirred for 30 min while allowing it to warm to room temperature. Evaporation of the solution to approximately 150 ml, followed by filtration and washing of the filter cake with cold water, yielded 8.3 g (83.5%) of yellow product, mp 196–198°. Purification by either crystallization from absolute ethanol or by sublimation gives a yield of 6.8 g (68%), mp 201–202°.

Anal. Calcd for $C_6H_9N_5O_3$: C, 36.2; H, 4.5; N, 35.2. Found: C, 36.1; H, 4.6; N, 35.1.

Methylpyridinium Salt of 1,6-Dihydro-4-hydroxy-1-methyl-5-nitro-6-oxopyrimidine (**11**).—In a 100-ml round-bottom flask were placed 1.027 g (0.0056 mol) of 4,6-dimethoxy-5-nitropyrimidine and 50 ml of anhydrous pyridine. The flask was fitted with a reflux condensor and heated in an oil bath maintained at 135–140°, for about 40 min, with stirring. On cooling overnight in a refrigerator, the salt precipitated as a brown crystalline solid. The mixture was filtered with suction, and the solid was washed with fresh pyridine and dried *in vacuo* at about 80° for 24 hr, yielding 0.379 g (25.8%) of the light brown salt: mp 155–157°; ir (Nujol) 3067 (aromatic hydrogen), 1655 (cyclic amide CO), 1618 (aromatic ring), 1595, 1330 (nitro); nmr (D_2O) δ 3.45 (s, 3), 4.51 (s, 3), 8.10 (m, 3), 8.53 (m, 1), 8.87 ppm (m, 2).

Anal. Calcd for $C_{11}H_{12}N_4O_4$: C, 49.99; H, 4.59. Found: C, 49.81; H, 4.56.

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1,6-Dihydro-4-hydroxy-1-methyl-5-nitro-6-oxopyrimidine (12).—To 0.379 g of the methylpyridinium salt of 1,6-dihydro-4-hydroxy-1-methyl-5-nitro-6-oxopyrimidine was added 5 ml of dilute hydrochloric acid, whereupon a tan precipitate formed immediately. The mixture was refrigerated for several hours and then filtered with suction. Recrystallization of the solid from water yielded 0.118 g (43.3%) of 1,6-dihydro-4-hydroxy-1-methyl-5-nitro-6-oxopyrimidine: mp 265–269° dec; ir (Nujol) 3085 (hydrogen bonded OH), 1684 (cyclic amide CO), 1513, 1340 (nitro); nmr (D_2O) δ 9.03 (s, 1), 3.62 ppm (s, 3).

Anal. Calcd for $C_5H_5N_3O_4$: C, 35.09; H, 2.95. Found: C, 34.83; H, 2.89.

4-Hydroxy-6-methoxy-5-nitropyrimidine (13).—A solution of 1.85 g (0.01 mol) of 4,6-dimethoxy-5-nitropyrimidine in 50 ml of pyridine was refluxed for 30 min. After filtration of the insoluble salt (the methylpyridinium salt of 1,6-dihydro-4-hydroxy-1-methyl-5-nitro-6-oxopyrimidine), 1.03 g (38.8%), the pyridine was removed by vacuum distillation. The resulting dark oil was dissolved in 15 ml of cold water and acidified with glacial acetic acid. The light yellow precipitate was isolated by filtration, washed with cold water, and dried to yield 0.47 g (27.4% yield based on the 4,6-dimethoxy-5-nitropyrimidine not accounted for by the insoluble salt), mp 242–243°. An infrared spectrum of the material was identical with the infrared spectrum of an authentic sample of 4-hydroxy-6-methoxy-5-nitropyrimidine.[7] The two compounds accounted for 66.2% of the starting material.

Anal. Calcd for $C_5H_5N_3O_4$: C, 35.1; H, 2.9. Found: C, 35.0; H, 2.9.

Methylpyridinium Salt of 4,6-Dihydroxy-5-nitropyrimidine.—To 50 ml of refluxing pyridine was added 1.71 g (0.01 mol) of 4-hydroxy-6-methoxy-5-nitropyrimidine. After 1 hr two immiscible layers separated which were then cooled in an ice bath. Upon being stirred the lower layer crystallized, yielding light brown crystals. The mixture was separated by filtration and the crystalline product was washed with fresh pyridine, yielding 1.62 g (65%) of the light brown salt, mp 147–148°.

Anal. Calcd for $C_{10}H_{10}N_4O_4$: C, 48.0; H, 4.0; N, 22.4. Found: C, 47.8; H, 3.9; N, 22.2.

The methylpyridinium salt of 4,6-dihydroxy-5-nitropyrimidine (1 g) in 15 ml of cold water was acidified with dilute hydrochloric acid until the solution was acidic to litmus paper, whereupon a white precipitate formed. Isolation of the precipitate yielded 0.54 g (86.3%) which was identified from infrared spectra and C, H, and N analysis as 4,6-dihydroxy-5-nitropyrimidine, mp <300°.

Anal. Calcd for $C_4H_3N_3O_4$: C, 30.6; H, 1.9; N, 26.8. Found: C, 30.5; H, 1.9; N, 26.7.

To the mother liquor from the preparation of the methylpyridinium salt of 4,6-dihydroxy-5-nitropyrimidine was added 0.64 ml (0.04 mol) of methylhydrazine. The solution was refluxed for 30 min and isolation yielded 0.076 g (17.3% based on the 4-hydroxy-6-methoxy-5-nitropyrimidine not accounted for by the salt) of 4-hydrazino-6-hydroxypyrimidine as judged by comparison of infrared spectra.

Volatile By-products Evolved from Reaction of Methylhydrazine, 4,6-Dimethoxy-5-nitropyrimidine, and Pyridine and Butanol Solvents. A. Amines.—To 1.85 g (0.01 mol) of 4,6-dimethoxy-5-nitropyrimidine in 50 ml of pyridine heated under reflux was added 1.84 ml (0.04 mol) of methylhydrazine. The system was flushed with nitrogen gas. The volatiles from the reaction system were first passed through a salt–ice cold trap and then into 100 ml of 0.1 *N* hydrochloric acid. The acid was back titrated with 0.1 *N* sodium hydroxide; 33.60 ml of sodium hydroxide were required. This accounts for 0.00664 mol of amine vapors. The yield of 4-hydrazino-6-hydroxypyrimidine was 0.708 g (56.2%).

B. Methyl Nitrite. 1.—The 4,6-dimethoxy-5-nitropyrimidine–methylhydrazine reaction in pyridine was carried out as described previously. The volatiles from the reaction were passed through a double U-tube. In the first U-tube was placed a strip of starch–iodide test paper wetted with distilled water; in the second was placed a strip of starch–iodide test paper wetted with dilute hydrochloric acid. During the reaction the first strip of test paper remained white while the second strip started turning dark purple after about 5 min of reflux (simultaneous with the first appearance of precipitation in the reaction vessel).

2.—A reaction was carried out with methylhydrazine and 4,6-dimethoxy-5-nitropyrimidine in pyridine. The system was first flushed with nitrogen gas and then the reactants were added. The usual scale of 0.01 mol of 4,6-dimethoxy-5-nitropyrimidine was used. To ensure the removal of any amines or pyridine vapors, the gaseous products were passed through a calcium chloride tube and two U-tubes cooled in salt–ice bath prior to trapping in the Schwartz tube. A soda–lime tube and a drierite tube were used to prevent carbon dioxide or water from condensing into the Schwartz tube. After the reflux period the Schwartz tube was sealed off and attached to a vacuum line. The material in the tube was then transferred by normal techniques to a gas infrared cell. The spectrum was then obtained using a Beckman IR-7 spectrophotometer. This spectrum accounted for the presence of methyl nitrite as well as another extremely volatile compound, possibly cyanic acid.

C. Methanol and Methyl-*n*-butyl Ether.—To 1.85 g (0.01 mol) of 4,6-dimethoxy-5-nitropyrimidine in 100 ml of 1-butanol was added 1.84 ml (0.04 mol) of methylhydrazine. The solution was refluxed for 3 hr and then cooled in an ice bath. The 4-hydrazino-6-hydroxypyrimidine, 0.24 g (19% yield), was removed by filtration. The mother liquor was analyzed by gas chromatographic techniques which revealed the presence of methanol, methyl *n*-butyl ether, methylhydrazine, and 1-butanol.

Registry No.—**1**, 15846-14-7; **2**, 29939-34-2; **3**, 29939-35-3; **4**, 29939-36-4; **5**, 29939-37-5; **6**, 29939-38-6; **7**, 29939-39-7; **8**, 1193-22-2; **9**, 29939-41-1; **10**, 29954-19-6; **11**, 29954-20-9; **12**, 29954-21-0; **13**, 14341-20-9; **14**, 29954-23-2; **15**, 2164-83-2; 4-chloro-6-hydroxy-2-phenylpyrimidine, 29954-25-4; methylhydrazine, 60-34-4.

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