To 2.5 g. (0.0075 mole) of fraction "F" dissolved in 25 cc. of ethanol was added 0.70 g. (0.0075 mole) of methyl bromide. The precipitate was separated by filtration; yield 1.8 g. (56%), m.p. 315–316° dec.

Anal. Calcd. for $C_{21}H_{27}BrN_2O$: Br, 19.83; N, 6.94. Found: Br, 19.93; N, 7.07.

MILWAUKEE 1, WISCONSIN

[CONTRIBUTION FROM THE WELLCOME RESEARCH LABORATORIES]

Studies on Condensed Pyrimidine Systems. XII. Synthesis of Some 4- and 2,4-Substituted Pyrido[2,3-d]pyrimidines

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RECEIVED NOVEMBER 16, 1954

2-Aminonicotinic acid reacts with formamide, urea and thiourea to yield 4-hydroxy-(I), 2,4-dihydroxy-(IX) and 2-mercapto-4-hydroxy-(VI) pyrido[2,3-d]pyrimidines, respectively. These substances serve as starting materials for transformation reactions leading to a variety of pyrido-[2,3-d]pyrimidines with one or two functional groups in the pyrimidine moiety. Some similarities and differences between the pyrido[2,3-d]-pyrimidines and related quinazolines, pteridines and purines are pointed out.

The present investigation of pyrido(2,3-*d*)-pyrimidines was undertaken in connection with studies in this Laboratory of various pyrimidines and condensed pyrimidine systems as antagonists of the heterocyclic constituents of the nucleic acids[2], and of the folic–folinic acid family of vitamins.[3] Prior to this work a few derivatives of pyrido-(2,3-d)pyrimidine were known. Klisiecki and Sucharda[4] claim to have prepared 4-hydroxypyrido-(2,3-d)pyrimidine (I) from 2-aminonicotinic acid and formamide. McLean and Spring[5] prepared 2,4-dihydroxypyrido(2,3-d)pyrimidine (IX) from quinolinic acid amide and sodium hypobromite. The structure of this compound was established by degradation to 2-aminonicotinic acid. These workers also obtained 2,4-dichloropyrido(2,3-d)-pyrimidine (XIV) from IX by chlorination with phosphorus oxychloride.

Attempts to prepare 4-hydroxypyrido(2,3-d)-pyrimidine (I) from 2-aminonicotinic acid and formamide according to the directions of Klisiecki and Sucharda[4] resulted only in the recovery of a small amount of 2-aminonicotinic acid; the product described as melting above 385° was not obtained in any experiment. By increasing the amount of formamide and altering the reaction time, temperature and isolation procedure, a yield of over 70% of a product, m.p. 258°, could be obtained. This product analyzed correctly for 4-hydroxypyrido(2,3-d)pyrimidine (I) and possessed all the expected properties of this compound.

The synthesis of 2,4-dihydroxypyrido(2,3-d)-pyrimidine (IX) from the diamide of quinolinic acid was repeated in this Laboratory following the directions of McLean and Spring.[5] The utility of this was limited by the low yield of the intermediate. A search for another route led to the finding that the fusion of urea with 2-aminonicotinic acid gave IX in yields greater than 60% of the theoretical.

The need for rather large amounts of 2-aminonicotinic acid to prepare both I and IX resulted in a new preparation of this acid from the commercially available 2-amino-3-methylpyridine through oxidation of the acetyl derivative with potassium permanganate.

The reactions of 4-hydroxy- (I) and 2,4-dihydroxypyrido(2,3-d)pyrimidine (IX) with phosphoryl chloride and phosphorus pentasulfide provided chloro and mercapto derivatives which served as intermediates for a variety of transformation reactions. Thus 4-chloropyrido(2,3-d)pyrimidine (II) reacted readily with ammonia, diethylamine, aniline and hydrazine to give the 4-amino-(III), diethylamino- (VIII), anilino and hydrazino (IV) derivatives, respectively. The 2,4-dichloro derivative (XIV) readily yields various diamino derivatives (XIII, XVII, XVIII). It resembles 2,4-dichloroquinazoline[6] in the selective replacement of the 4-chloro group under mild conditions. This led to the preparation of the 2-chloro-4-hydroxy (XI), 2-chloro-4-amino (XV) and 2-chloro-4-mercapto (XIX) derivatives.

Many of the derivatives were interrelated by transformation reactions which served to establish the structures. The allocation of functional groups in 2-chloro-4-hydroxypyrido(2,3-d)pyrimidine was established by its conversion to the 2-mercapto-4-hydroxy (VI) derivative which was also prepared in a definitive manner from 2-aminonicotinic acid and thiourea. The isomeric 2-hydroxy-4-mercapto derivative was obtained by hydrolysis of the 2-chloro-4-mercapto compound, providing confirmation of the structure assigned to these two derivatives. Mono- and dimercapto derivatives also could be prepared by treatment of the hydroxy derivatives with phosphorus pentasulfide. The dimercapto derivative (X) yielded the 2-mercapto-4-amino derivative (VII) which was hydrolyzed to VI, and, by treatment with Raney nickel, con-

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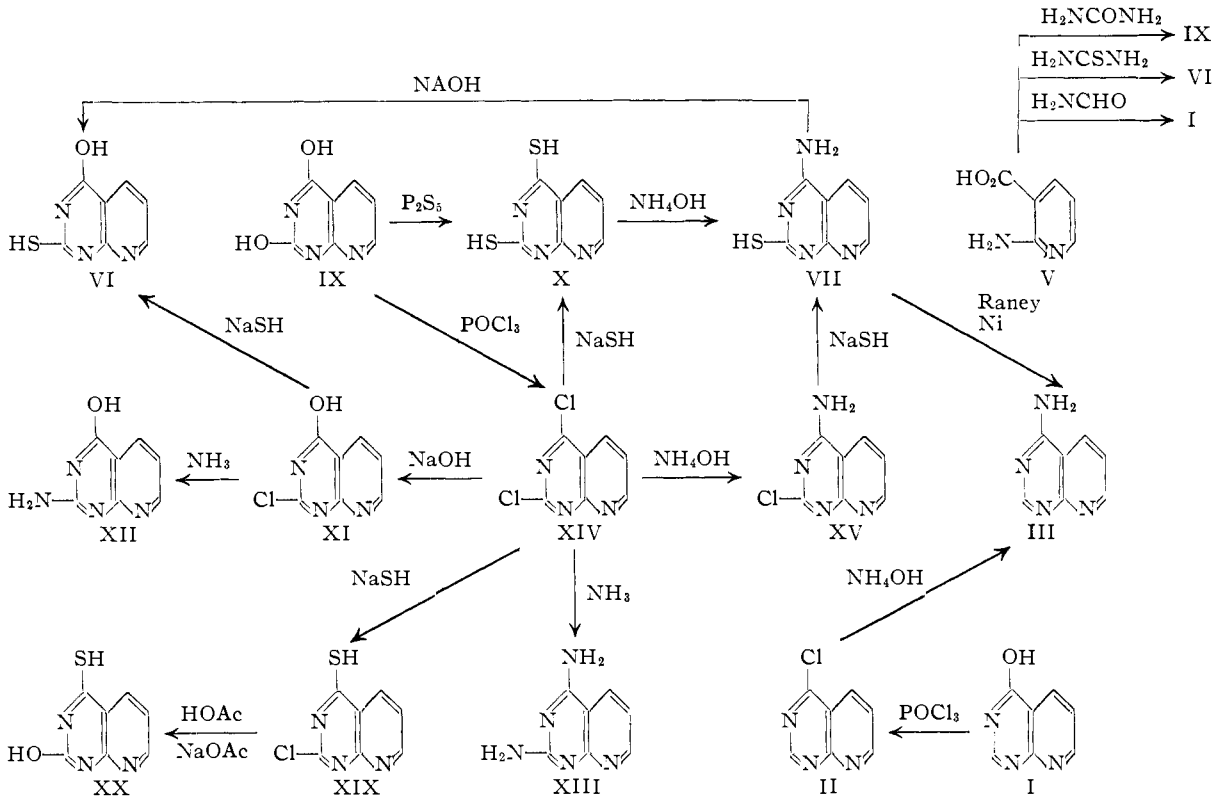

REACTION SCHEME

verted to the 4-amino derivative (III). The 2-mercapto-4-amino derivative also was prepared from the 2-chloro-4-amino derivative and sodium hydrosulfide.

It is evident from the foregoing descriptive material that the chemical reactions of the pyrido-(2,3-d)pyrimidines are similar in many respects to those of pyrimidines, and condensed pyrimidine systems such as quinazolines, pteridines and purines. A few analogies and contrasts may be worthy of comment. The chlorination of the hydroxyl derivatives is similar to those of pyrimidines and quinazolines and more readily accomplished than with the purines, and is in contrast to the instability of some pyridines and pteridines[7] to the halides of phosphorus. 2,4-Dichloropyrido-(2,3-d)pyrimidine allows selective replacement of the 4-chlorine atom. This behavior is similar to that of dichloroquinazoline but differs from that of the generality of pyrimidines. The 4-amino group in the pyrido(2,3-d)pyrimidine series is less stable than that of 6-aminopurines and 4-aminopyrimidines but perhaps somewhat more stable than in the pteridine series.[7] In general, the reactions of the pyrido(2,3-d)pyrimidines which have been investigated are those of the pyrimidine moiety, and in behavior the new substances occupy within reasonable limits a position intermediate between the quinazolines and pteridines as would be expected from structural considerations.

In physical properties, also, there are many points of resemblance between derivatives of the pyrido(2,3-d)pyrimidine system and those of other condensed pyrimidine systems. The amino, hydroxyl and mercapto derivatives decompose at high temperatures often without melting and show low solubilities in organic solvents. Albert, *et al.*,[7] have suggested that the high melting (decomposition) points and low solubilities of similar pteridine derivatives are the result of hydrogen bonding resulting in crystal lattice forces of unusual magnitude. They support this view by reference to the more "normal" properties of compounds in which the pertinent hydrogen atoms have been replaced by alkyl groups. Some comparisons in the pyrido(2,3-d)pyrimidine series are equally striking. Thus the 4-amino- derivative decomposes at 300°, the diethylamino derivative melts at 72–73°; 2,4-diaminopyrido(2,3-d)pyrimidine decomposes at 356° and the bis-dimethylamino derivative melts at 98°.

The ultraviolet absorption spectra of the pyrido-(2,3-d)pyrimidines (Table I) are characteristic but resemble those of the corresponding pteridines rather closely (*cf.* 7–9) with a less close correspondence to the quinazolines.[10] In dilute aqueous solution, 2,4-diaminopyrido(2,3-d)pyrimidine has a blue-violet fluorescence which superficially resembles those of related pteridine derivatives.

Acknowledgment.—The authors wish to thank S. W. Blackman, N. Martinez, Jr., and Pauline Kulka for the microanalyses reported here.

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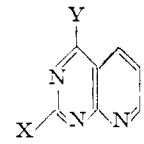
TABLE I

ULTRAVIOLET ABSORPTION SPECTRA OF PYRIDO(2,3-d)PYRIMIDINES



X	Y	pH 1.0 λmax, mμ	pH 1.0 Em × 10⁻³	pH 1.0 λmin, mμ	pH 1.0 Em × 10³	pH 11.0 λmax, mμ	pH 11.0 Em × 10⁻³	pH 11.0 λmin, mμ	pH 11.0 Em × 10³
H	OH	270	4.18	245	2.1	280	4.12	252	2.6
		317	7.95	280	3.8	313	7.43	290	3.9
OH	OH	305	8.0	260	1.0	263	9.15	280	2.2
						310	8.97		
H	NH_2	313	13.7	275	2.2	280–287[a]	4.13	255	3.0
						318	9.06		
Cl	NH_2	248	9.77	290	1.8	273	4.55	260	4.1
		348	7.7			317	7.67	288	3.8
NH_2	OH	273	11.7	255	5.6	265	7.38	258	6.9
		342	7.55	290	1.8	328	6.45	290	1.6
NH_2	NH_2	266	6.13	287	3.7	245	17.0	290	1.7
		313	8.15			265[a]	6.9		
						340	6.13		
H	SH	255	9.1	285	1.6	240	11.7	292	1.6
		385	8.46			370	10.0		
SH	OH	283	23.8	304	10	298	20.9		
		317	11.1						
Cl	SH	258	8.5	290	3.0	245	12.0		
		375	10.2			270[a]	7.2		
						373	12.9		
OH	SH	275–288	11.3			267	8.15	280	6.8
		320–360[a]	7.0			305	11.9		
						350–380[a]	4.9		
SH	SH	234	10.0	250	7.8	235	13.6	255	10.7
		273	15.4	282	14	265	11.3	282	8.7
		293	15.1	315	9.8	307	19.5	355	7.2
		340	10.9			385	8.6		

[a] Inflection.

This work was supported by a grant from the Charles F. Kettering Foundation.

Experimental[11]

Preparation of 2-Aminonicotinic Acid (V).—To 13 liters of water at 70° was added 100 g. of 2-acetylamino-3-methylpyridine prepared by the method of Seide[12] from 2-amino-3-methylpyridine. Then to the efficiently stirred solution was added all at once, a solution of 250 g. of potassium permanganate. The temperature of the reaction mixture was maintained between 70–75° with continued stirring until the potassium permanganate was completely decolorized, approximately 6 hours. After filtration of the manganese dioxide, the colorless filtrate was evaporated to dryness on the steam-bath. The solid was dissolved in 500 ml. of water, the solution was neutralized by the addition of concentrated hydrochloric acid; 100 ml. in excess was then added. The solution was vigorously boiled for 15 minutes, cooled and concentrated ammonium hydroxide added to give a *p*H value of about 5. After standing overnight in the refrigerator, the mixture was filtered and the precipitate washed with cold water and dried at 120°. Yield of colorless 2-aminonicotinic acid was 54–59 g., m.p. 308–310°. Philips[13] reports m.p. of 2-aminonicotinic acid as 310°.

Anal. Calcd. for $C_6H_6N_2O_2$: C, 52.3; H, 4.40; N, 20.3. Found: C, 52.8; H, 4.70; N, 20.6.

The ultraviolet absorption spectrum showed $\lambda_{max.}$ at 243 and 325 mμ at *p*H 1 and $\lambda_{max.}$ at 243 and 312 mμ at *p*H 11.

4-Hydroxypyrido(2,3-d)pyrimidine (I).—Fifty grams of 2-aminonicotinic acid and 100 g. of formamide were heated at 165–170° (inside temperature) by means of an oil-bath for 2.5 hours. After cooling, the solid was collected and recrystallized from 700 ml. of hot water to yield 37.5 g. of colorless plates, m.p. 255–257°. A second recrystallization from water raised the melting point to 258°.

Anal. Calcd. for $C_7H_5N_3O$: C, 57.0; H, 3.40; N, 28.6. Found: C, 56.9; H, 3.40; N, 28.4.

2,4-Dihydroxypyrido(2,3-d)pyrimidine (IX).—50.0 grams of 2-aminonicotinic acid and 90 g. of urea were finely ground and heated together in a casserole until the temperature of the melt reached 180–190°. After 15 minutes the temperature was gradually raised to 200° and the clear melt became mushy. The temperature was raised carefully to 210° and the heating discontinued. The cooled melt was dissolved in 500 ml. of 2 *N* sodium hydroxide by warming and the warm solution was saturated with carbon dioxide, cooled and filtered and the precipitate washed with water. The yield was 35.2 g. of 2,4-dihydroxypyrido(2,3-d)pyrimidine, m.p. 360°. A small amount was recrystallized from glacial acetic acid, m.p. 365°.

Anal. Calcd. for $C_7H_5N_3O_2$: N, 25.8. Found: N, 25.9.

The ultraviolet absorption spectrum of this compound was found to be identical with that of a sample of 2,4-dihydroxypyrido(2,3-d)pyrimidine prepared according to the directions of McLean and Spring.[5] Mixed m.p. of the two samples was 364–365°.

2,4-Dichloropyrido(2,3-d)pyrimidine (XIV).—This compound was prepared essentially according to the directions of McLean and Spring.[5] However, the exact procedure employed in the preparation of this important intermediate on a much larger scale is described here. Twenty grams of 2,4-dihydroxypyrido(2,3-d)pyrimidine (IX) was added to 400 ml. of phosphorus oxychloride and the mixture refluxed until solution was effected (15–20 hours). The excess phosphorus oxychloride was removed under reduced pressure and the sirupy residue poured onto 400 g. of crushed ice. The cold aqueous solution was extracted immediately with chloroform (3 × 300 ml.). The combined chloroform ex-

(11) All melting points are uncorrected.

(12) O. Seide, *Ber.*, **57**, 1804 (1924).

(13) A. Philips, *ibid.*, **27**, 840 (1894).

tracts were washed by shaking with 100 ml. of water and then dried over anhydrous magnesium sulfate. Evaporation of the chloroform on the steam-bath yielded 21.0 g. of 2,4-dichloropyrido(2,3-d)pyrimidine, m.p. 157–158° dec. Recrystallization from Skellysolve "C" raised the melting point to 158–158.5°. McLean and Spring[5] record 156–157° as the melting point of this compound.

4-Chloropyrido(2,3-d)pyrimidine (II).—To 300 ml. of phosphorus oxychloride was added 20.0 g. of 4-hydroxypyrido(2,3-d)pyrimidine (I) and the solution was refluxed for one hour. (There remained a small amount of tarry material which did not dissolve with longer refluxing.) The excess phosphorus oxychloride was removed under reduced pressure and the sirupy residue was poured onto ice. The solution was then extracted with chloroform and the 4-chloropyrido(2,3-d)pyrimidine isolated as in the preparation of 2,4-dichloropyrido(2,3-d)pyrimidine (XIV). The yield of crude product was 9.8 g., m.p. 135° dec. (43.7%). A small amount was recrystallized from Skellysolve "C" to raise the melting point to 137° dec.

Anal. Calcd. for $C_7H_4N_3Cl$: N, 25.4. Found: N, 25.5.

4-Aminopyrido(2,3-d)pyrimidine (III). **Method** (A).—To 50 ml. of concentrated ammonium hydroxide was added 5.0 g. of crude 4-chloropyrido(2,3-d)pyrimidine (II) and the solution was heated for 45 minutes on the steam-bath, decolorized with norite and filtered. The filtrate was cooled in an ice and salt bath, saturated with ammonia gas and filtered to yield 3.1 g. of 4-aminopyrido(2,3-d)pyrimidine as colorless needles. Recrystallization from 95% isopropyl alcohol–water mixture gave colorless needles, m.p. 299–301° dec. (when placed in the block at 280° and heated rapidly).

Anal. Calcd. for $C_7H_6N_4$: C, 57.5; H, 4.15; N, 38.4. Found: C, 57.2; H, 4.29; N, 38.4.

4-Aminopyrido(2,3-d)pyrimidine (III). **Method** (B).—Three hundred milligrams of 2-mercapto-4-aminopyrido-(2,3-d)pyrimidine (VII) was dissolved in a solution of 1 liter of 95% ethanol and 50 ml. of concentrated ammonium hydroxide. Approximately 1 g. of Raney nickel W 4 was added and the solution was refluxed for three hours, filtered and evaporated to dryness on the steam-bath. The residue was extracted with 50 ml. of water and the aqueous solution evaporated to yield 110 mg. of colorless needles, m.p. 280–290° dec. Recrystallization from 95% isopropyl alcohol raised the m.p. to 297–300° dec. Mixed m.p. with III, method (A) was 297–300° dec. Ultraviolet absorption spectra of III method (A) and method (B) were identical.

2,4-Diaminopyrido(2,3-d)pyrimidine.—To 20 ml. of absolute ethanol saturated at 0° with dry ammonia was added 6.5 g. of crude 2,4-dichloropyrido(2,3-d)pyrimidine (XIV), and the solution was heated in a bomb at 150° for 12 hours. After cooling, 30 ml. of water and 10 ml. of 2 *N* sodium hydroxide were added, the solution was warmed and then allowed to stand 5 hours at 5°. The precipitate was filtered, washed with a little water and recrystallized from 500 ml. of a 50% ethanol–water mixture to which had been added 0.5 ml. of 2 *N* sodium hydroxide. The chilled solution yielded 3.9 g. of colorless needles, m.p. 356° dec.

Anal. Calcd. for $C_7H_7N_5$: C, 52.5; H, 4.25; N, 43.5. Found: C, 52.6; H, 4.64; N, 43.7.

2-Chloro-4-hydroxypyrido(2,3-d)pyrimidine (XI).—Three grams of finely pulverized 2,4-dichloropyrido(2,3-d)pyrimidine (XIV) was added to 75 ml. of 1 *N* sodium hydroxide at room temperature. When the 2,4-dichloropyrido(2,3-d)pyrimidine had dissolved, a small amount of carbon was added and the solution allowed to stand 15 minutes at room temperature. The solution was then filtered, cooled and acidified with glacial acetic acid. Upon standing overnight at 5° the solution yielded 2.4 g. of tan needles. The compound did not melt below 360°.

Anal. Calcd. for $C_7H_4N_3OCl$: C, 46.3; H, 2.2; N, 23.1. Found: C, 46.2; H, 2.21; N, 23.4.

2-Amino-4-hydroxypyrido(2,3-d)pyrimidine (XII).—In a glass-lined bomb was placed 3.1 g. of 2-chloro-4-hydroxypyrido(2,3-d)pyrimidine and 20 ml. of alcoholic ammonia. The bomb was heated to 150° for 15 hours. The solution was then diluted with 80 ml. of water, cooled, filtered and washed with cold water. The yield of almost colorless 2-amino-4-hydroxypyrido(2,3-d)pyrimidine was 2.4 g., m.p. above 360°.

Anal. Calcd. for $C_7H_5N_4O$: C, 51.8; H, 3.70; N, 34.6. Found: C, 52.2; H, 3.86; N, 34.5.

4-Diethylaminopyrido(2,3-d)pyrimidine (VIII).—Three grams of 4-chloropyrido(2,3-d)pyrimidine (II) was dissolved in 150 ml. of dry dioxane, 30 ml. of diethylamine was added and the solution allowed to remain overnight in the refrigerator. The diethylamine hydrochloride was filtered off and the excess dioxane and diethylamine were evaporated on the steam-bath. The gummy residue was extracted several times with Skellysolve "B." Concentration of the combined solution yielded on cooling 0.7 g. of almost colorless crystals, m.p. 70–72°. A second recrystallization from the same solvent raised the m.p. to 72–73°.

Anal. Calcd. for $C_{11}H_{14}N_4$: C, 63.4; H, 7.40. Found: C, 63.5; H, 7.40.

4-Anilinopyrido(2,3-d)pyrimidine.—One gram of 4-chloropyrido(2,3-d)pyrimidine (II) was carefully added to a solution of one gram of aniline in 10 ml. of water. The solution was heated for 30 minutes on the steam-bath, made basic with concentrated ammonium hydroxide, cooled and filtered. The crude precipitate was recrystallized from 95% ethanol. A second recrystallization from the same solvent gave 0.51 g. of light green needles, m.p. 256–257°.

Anal. Calcd. for $C_{13}H_{10}N_3$: C, 70.3; H, 4.52; N, 25.2. Found: C, 70.6; H, 4.48; N, 25.5.

2-Chloro-4-aminopyrido(2,3-d)pyrimidine (XV).—Ten grams of 2,4-dichloropyrido(2,3-d)pyrimidine (XIII) was finely powdered and suspended in 300 ml. of concentrated ammonium hydroxide. The mixture was heated on the steam-bath for two hours, cooled and filtered. The slightly yellow precipitate was extracted with 200 ml. of 1 *N* sodium hydroxide for one-half hour to remove any unreacted starting material, and washed repeatedly with water. The yield was 8.1 g. The compound decomposed when heated above 310°. No suitable recrystallization solvent could be found.

Anal. Calcd. for $C_7H_5N_4Cl$: C, 46.6; H, 2.78; N, 31.0. Found: C, 46.6; H, 2.93; N, 31.5.

2,4-Dimercaptopyrido(2,3-d)pyrimidine. Method (A).—Four grams of 2,4-dichloropyrido(2,3-d)pyrimidine (XIV) was dissolved in 150 ml. of 4 *N* sodium hydrosulfide. The solution was warmed for 15 minutes on the steam-bath, diluted with 100 ml. of water, cooled and acidified with acetic acid. The yellow-green precipitate was filtered and dried at 130° to yield 3.5 g. melting above 360°. A small amount was purified for analysis by dissolving in dilute sodium hydroxide and precipitating with acetic acid.

Anal. Calcd. for $C_7H_5N_3S_2$: C, 43.0; H, 2.58; N, 21.5. Found: C, 43.6; H, 2.92; N, 21.4.

Method (B).—Twenty grams of 2,4-dihydroxypyrido-(2,3-d)pyrimidine (VII), 100 g. of finely pulverized phosphorus pentasulfide and 500 ml. of tetralin were heated for two hours at 200–205° (inside temperature). The solution was cooled, filtered and the precipitate washed with skellysolve "B." The precipitate was dissolved in 600 ml. of cold 3 *N* sodium hydroxide and the solution was then acidified with an excess of acetic acid and filtered. The yellow-green precipitate was washed and dried at 130° to yield 23 g. of product identical with that obtained by method (A) (ultraviolet absorption spectrum).

4-Mercaptopyrido(2,3-d)pyrimidine.—Twenty-three grams of 4-hydroxypyrido(2,3-d)pyrimidine (I), 100 g. of pulverized phosphorus pentasulfide and 500 ml. of tetralin were heated to 175–180° (inside temperature) for 1.5 hours with initial stirring. The cooled reaction mixture was filtered and worked up in a manner identical to that employed in the preparation of 2,4-dimercaptopyrido(2,3-d)pyrimidine, method (B).

The crude green product was purified by Soxhlet extraction using absolute ethanol to yield 11.2 g. of yellow green needles, m.p. above 360°.

Anal. Calcd. for $C_7H_5N_3S$: C, 51.5; H, 3.06; N, 25.8. Found: C, 52.0; H, 3.61; N, 25.7.

2-Mercapto-4-aminopyrido(2,3-d)pyrimidine (VI). **Method** (A).—Five grams of finely powdered 2,4-dimercaptopyrido(2,3-d)pyrimidine (IX) method (B), was added to 150 ml. of concentrated ammonium hydroxide and the solution heated on the steam-bath for two hours. The starting material soon dissolved and after 15 to 20 minutes a precipitate was noted. The solution was filtered while hot. The product was suspended in concentrated ammo-

nium hydroxide and heated for one hour on the steam-bath. The solution was filtered hot and washed with a little cold aqueous ammonia. The yield of fine yellow-green needles was 3.5 g., dec. above 300°.

Anal. Calcd. for $C_7H_6N_4S$: C, 47.2; H, 3.37. Found: C, 47.3; H, 3.46.

Method (B).—Two and three-tenths grams of finely powdered 2-chloro-4-aminopyrido(2,3-d)pyrimidine (XV) was added slowly to a solution of 4 *N* sodium hydrosulfide and the solution was heated on the steam-bath for 2 hours while hydrogen sulfide was slowly bubbled through the solution. The solution was filtered and acidified with acetic acid while hot. Yield was 1.5 g. yellow-orange needles. The ultraviolet absorption spectrum was identical to that of the substance prepared by method (A).

4-Hydrazinopyrido(2,3-d)pyrimidine (IV).—Two grams of 4-chloropyrido(2,3-d)pyrimidine (II) was added with cooling to 30 ml. of an aqueous solution of hydrazine. The solution was then heated for 30 minutes on the steam-bath and set aside overnight to crystallize. The crude precipitate was filtered, washed with a little ice-water and recrystallized from absolute ethanol to give orange-red needles, m.p. 164–166°. Yield was 1.0 g.

Anal. Calcd. for $C_7H_7N_5$: C, 52.15; H, 4.35; N, 43.5. Found: C, 52.1; H, 4.41; N, 43.7.

The 2-Mercapto-4-hydroxypyrido(2,3-d)pyrimidine (VI). Method (A).—Twenty grams of 2-aminonicotinic acid and 30 g. of thiourea were heated together to 200° (temperature of melt). The clear yellow melt thickened as the temperature was gradually raised to 210° and after 5 minutes at 210° the heating was discontinued. The melt was dissolved in dilute sodium hydroxide, diluted to 350 ml. and saturated with carbon dioxide while hot. The solution was then cooled, filtered and the precipitate was washed with cold water; yield 5.0 g. The product was purified by solution in dilute sodium hydroxide followed by acidification with acetic acid. There was obtained 2.3 g. of colorless powder, m.p. 355–356°.

Anal. Calcd. for $C_7H_5N_3OS$: C, 47.0; H, 2.79; N, 23.45. Found: C, 47.6; H, 2.79; N, 23.6.

Method (B).—Three hundred milligrams of 2-chloro-4-hydroxypyrido(2,3-d)pyrimidine (XI) was warmed with 5 ml. of 2 *N* sodium hydrosulfide on the steam-bath. The solution was filtered and acidified with acetic acid and the crude precipitate purified by solution in dilute sodium hydroxide and precipitation from the hot solution with acetic acid. Yield was 230 milligrams, m.p. and mixed m.p. with X, method (A) was 355–356°. Ultraviolet absorption spectra of the two products method (A) and method (B) were identical.

Method (C).—2-Mercapto-4-aminopyrido(2,3-d)pyrimidine (0.5 g.) was suspended in 25 ml. of 2 *N* sodium hydroxide and the solution refluxed 2.5 hours. The solution was acidified with acetic acid and the precipitate filtered and washed with water. Yield was 0.42 g. This product was identical to that obtained by methods (A) and (B) as judged by mixed m.p. and ultraviolet absorption data.

2,4-Diphenoxypyrido(2,3-d)pyrimidine.—To a cooled solution of 3 g. of potassium hydroxide in 30 ml. of 95% phenol was added 4.0 g. of 2,4-dichloropyrido(2,3-d)pyrimidine (XIV) over a period of 10 minutes. The reaction mixture was maintained at 40–50° during this addition and then gradually heated to 80°. The solution was cooled, poured into 200 ml. of 2 *N* sodium hydroxide, filtered and washed with cold water. The crude precipitate was recrystallized from 95% ethanol to yield 2.6 g. of white needles, m.p. 203–205°.

Anal. Calcd. for $C_{19}H_{13}N_3O_2$: C, 72.4; H, 4.16; N, 13.3. Found: C, 72.5; H, 4.56; N, 13.6.

2,4-Dianilinopyrido(2,3-d)pyrimidine (XVIII).—To 25 ml. of water and 5 g. of aniline was added carefully with shaking 2.0 g. of 2,4-dichloropyrido(2,3-d)pyrimidine (XIV) and the solution was heated for 3 hours on the steam-bath. The solution was made basic with concentrated ammonium hydroxide, filtered and the precipitate washed once with cold ethanol. This crude product was suspended in 100 ml. of hot normal sodium hydroxide and enough alcohol added to effect solution. Upon cooling 2.1 g. of light green needles, m.p. 235–237°, was isolated. The compound was recrystallized from an ethanol–water mixture with no change in melting point.

Anal. Calcd. for $C_{19}H_{15}N_5$: C, 72.8; H, 4.80. Found: C, 72.5; H, 4.67.

2,4-Bis-(dimethylamino)-pyrido(2,3-d)pyrimidine (XVII).—To 30 ml. of a 25% solution of aqueous dimethylamine was added 5.0 g. of 2,4-dichloropyrido(2,3-d)pyrimidine (XIV) and the solution was heated 2 hours on the steam-bath and then allowed to evaporate to dryness. The residue was dissolved in 200 ml. of water and the solution made strongly basic with sodium hydroxide and extracted twice with 200 ml. of chloroform. The chloroform was washed with water and dried over anhydrous magnesium sulfate. Evaporation of the chloroform left a brown oil which solidified on cooling. The product was purified by extraction of this residue with several portions of boiling heptane which after concentration and cooling yielded 2.9 g. of white crystals, m.p. 95–97°. Recrystallization from the same solvent raised the m.p. to 97–99°.

Anal. Calcd. for $C_{11}H_{15}N_5$: C, 60.8; H, 6.90; N, 32.3. Found: C, 61.0; H, 6.87; N, 32.5.

2,4-Dihydrazinopyrido(2,3-d)pyrimidine.—To 20 ml. of 85% hydrazine was added in small portions 5.0 g. of 2,4-dichloropyrido(2,3-d)pyrimidine (XIV). The solution was heated for 2 hours on the steam-bath, cooled, filtered. The product was washed with ethanol and purified by Soxhlet extraction using absolute ethanol as a solvent. Yield of small orange needles was 1.6 g., m.p. 348–350° dec.

Anal. Calcd. for $C_7H_9N_7$: C, 44.0; H, 4.70; N, 51.4. Found: C, 44.3; H, 4.65; N, 52.6.

2-Anilino-4-hydroxypyrido(2,3-d)pyrimidine (XVI).—To 0.5 g. of aniline in 25 ml. of water was added 0.5 g. of 2-chloro-4-hydroxypyrido(2,3-d)pyrimidine (X). The solution was heated 1 hour on the steam-bath, cooled, made basic with sodium hydroxide and extracted with ether. The aqueous solution was acidified with acetic acid to yield 0.4 g. of light green product. Recrystallization from glacial acetic acid yielded light yellow-green needles, m.p. 350–352°.

Anal. Calcd. for $C_{13}H_{10}N_4O$: C, 65.5; H, 4.22; N, 23.5. Found: C, 64.9; H, 4.15; N, 23.8.

2-Chloro-4-mercaptopyrido(2,3-d)pyrimidine (XIX).—To 100 ml. of 0.4 *N* sodium hydrosulfide cooled to 0° was gradually added 2.0 g. of finely powdered 2,4-dichloropyrido-(2,3-d)pyrimidine (XIV). The solution was stirred at 0° for ½ hour and then carefully acidified with acetic acid, filtered and the precipitate washed with ice-water, cold ethanol and then ether. The yield was 1.6 g. of orange yellow solid, m.p. 327–330°.

Anal. Calcd. for $C_7H_4N_3SCl$: N, 21.3. Found: N, 21.5.

2-Hydroxy-4-mercaptopyrido(2,3-d)pyrimidine (XX).—To a solution of 100 ml. of water, 10 ml. of glacial acetic acid and 5 g. of sodium acetate was added 4.0 g. of 2-chloro-4-mercaptopyrido(2,3-d)pyrimidine (XIX). The solution was heated 15–20 minutes on the steam-bath, filtered and the orange precipitate washed with water and dried in the oven at 120°. The yield was 3.5 g., m.p. 294–296°.

Anal. Calcd. for $C_7H_5N_3SO$: C, 47.0; H, 2.79; N, 23.5. Found: C, 47.2; H, 2.51; N, 23.9.

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