4-Methylisoquinoline-N-oxide.—The oxide was prepared by the method employed for the 4-chloro compound. The material from the chloroform extracts was obtained as a hygroscopic solid of wide melting range. From 14.32 g. of 4-methylisoquinoline 14.62 g. of crude oxide was obtained. The analytical sample was recrystallized from chloroform (Darco) by adding hexane to the hot solution to the cloud point, and from toluene–hexane by the same procedure. The analytical sample was dried for 9 days *in vacuo* to constant melting point, m.p. 129–131°.

Anal. Calcd. for $C_{10}H_9NO$: C, 75.44; H, 5.71; N, 8.80. Found: C, 75.76; H, 5.62; N, 8.78.

Infrared Spectra.—All spectra were measured from KBr disks on either a Perkin–Elmer spectrophotometer or a Baird instrument by Dr. S. M. Nagy and associates at the Microchemical Laboratory, Massachusetts Institute of Technology.

AMHERST, MASSACHUSETTS

[CONTRIBUTION FROM THE WELLCOME RESEARCH LABORATORIES]

Studies on Condensed Pyrimidine Systems. XIX. A New Synthesis of Pyrido[2,3-d]pyrimidines. The Condensation of 1,3-Diketones and 3-Ketoaldehydes with 4-Aminopyrimidines

BY ROLAND K. ROBINS AND GEORGE H. HITCHINGS

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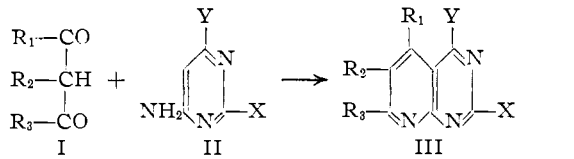
A number of 2,4-dihydroxy-, 2,4-diamino-, 2-amino-4-hydroxy- and 2-mercapto-4-hydroxypyrido[2,3-d]pyrimidines substituted in the pyridine ring has been prepared by the condensation of various 1,3-diketones and β-ketoaldehydes with the appropriate 4-aminopyrimidines in the presence of 85% phosphoric acid. The structures of representative compounds have been established by independent synthesis. When a β-ketoaldehyde is employed, the resulting condensation product is a 7-substituted pyrido[2,3-d]pyrimidine, indicating that the aldehyde group has condensed with the 5-position of the pyrimidine ring. Several 4-hydroxypyrido[2,3-d]pyrimidines have been prepared by treatment of the corresponding 2-mercapto-4-hydroxyl derivatives with Raney nickel.

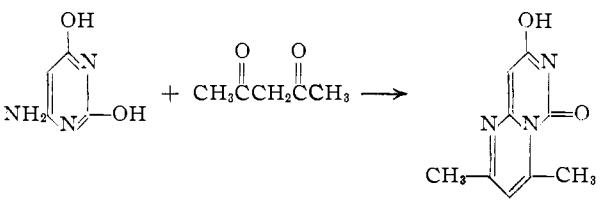
Studies in this Laboratory of pyrimidines,[1] condensed pyrimidine systems[2,3] and related substances[4,5] as inhibitors of nucleic acid biosynthesis[6,7] have been in progress for a number of years. Recently two series of carbocondensed pyridopyrimidines[8,9] were developed primarily to provide derivatives with a diversity of functional groups in the pyrimidine moiety. The investigations of Rydon and co-workers[10,11] followed similar lines. The previously reported synthetic methods employed pyridines as starting materials and were restricted in scope not only by the unavailability of many substituted pyridines but also by the limitations of the methods available for the formation of the pyrimidine moiety. The present method employs the condensation of a 4-aminopyrimidine with a β-diketone or β-ketoaldehyde to form pyrido[2,3-d]-pyrimidines. Since the pyrimidine and particularly the dicarbonyl reagent may be modified independently within rather wide limits, the synthesis of a considerable number of new substances has been possible.

The reaction takes the form



I II III

It might be anticipated that the course of the reaction would be affected by the nature of the substituents R_1, R_2 and R_3 of the dicarbonyl reagent and the nature of the functional groups X and Y of the pyrimidine. In preliminary experiments acetylacetone (I, R_1, R_3 = CH_3, R_2 = H) was heated with a solution of the pyrimidine in sirupy phosphoric acid. Products analyzing correctly for pyrido[2,3-d]pyrimidines were obtained with pyrimidines bearing hydroxyl, amino or mercapto groups in both the 2- and 4-position, but no product was obtained with either 2,4-diamino-6-methyl- or 6-amino-4-hydroxy-2-methylpyrimidine. Thus, the reactive pyrimidines appear to be those which have active 5-positions as judged by studies of nitrosation and coupling reactions.[12] Although the most probable course of the reaction was that formulated above, the possibility existed that the condensation might have occurred through the nitrogen of the pyrimidine ring to give a pyrimido-[1,2-c]pyrimidine derivative as



This possibility was eliminated and the structure

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(2) A. Maggiolo and G. H. Hitchings, THIS JOURNAL, **73**, 4226 (1951).

(3) G. B. Elion, E. Burgi and G. H. Hitchings, *ibid.*, **74**, 411 (1952).

(4) E. A. Falco, E. Pappas and G. H. Hitchings, *ibid.*, **78**, 1938 (1956).

(5) 3eme Congrès International de Biochimie, Rapports, p. 185, August 1–6, 1955.

(6) G. H. Hitchings, G. B. Elion, H. VanderWerff and E. A. Falco, *J. Biol. Chem.*, **174**, 765 (1948).

(7) G. H. Hitchings, *Am. J. Clin. Nutrit.*, **3**, 321 (1955).

(8) R. K. Robins and G. H. Hitchings, THIS JOURNAL, **77**, 2256 (1955).

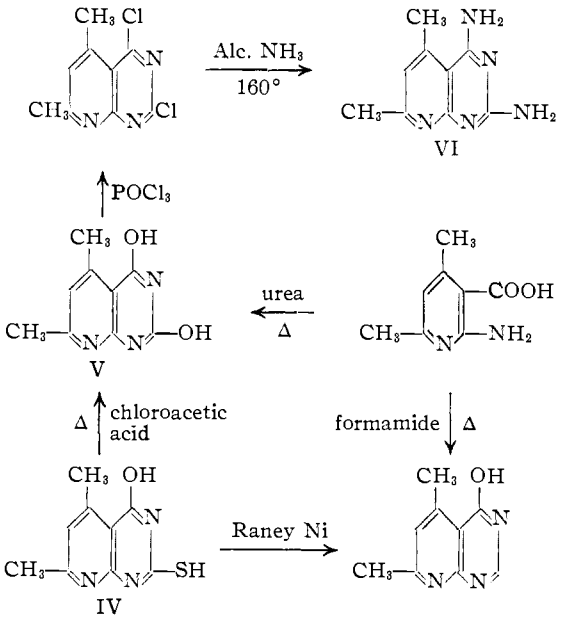
(9) R. K. Robins and G. H. Hitchings, *ibid.*, **78**, 973 (1956).

(10) V. Oakes, R. Pascoe and H. N. Rydon, *J. Chem. Soc.*, 1045 (1956).

(11) V. Oakes and H. N. Rydon, *ibid.*, 4433 (1956).

(12) B. Lythgoe, A. R. Todd and A. Topham, *ibid.*, 316 (1944).

of the products was established by the synthesis of 2,4-dihydroxy-5,7-dimethylpyrido[2,3-d]pyrimidine (III, $R_1 = R_3 = CH_3$; X = Y = OH) from 2-amino-4,6-dimethylnicotinic acid[13] by fusion with urea and the demonstration that this was indeed the substance obtained by the condensation of acetylacetone and 6-amino-2,4-dihydroxypyrimidine. The relationships among the 2,4-diamino-, 2-amino-4-hydroxy- and 4-hydroxypyrido[2,3-d]-pyrimidines, also synthesized by the condensation of acetylacetone with the appropriate pyrimidines, were established as shown in the reaction scheme



In addition, 5,7-dimethyl-4-hydroxypyrido[2,3-d]-pyrimidine was prepared by the alternate method from 2-amino-4,6-dimethyl-3-pyridinecarboxylic acid. Finally, 2,4-dihydroxypyrido[2,3-d]pyrimidine was synthesized from 6-aminouracil and shown to be identical to this substance as prepared earlier from 2-aminonicotinic acid.[8]

Variations in the dicarbonyl reagent were investigated next. It was soon discovered that alkylated derivatives of acetylacetone (pentane-2,4-dione) do not condense as well as acetylacetone itself. Thus, while acetylacetone gave 2,4-diamino-5,7-dimethylpyrido[2,3-d]pyrimidine when condensed with 2,4,6-triaminopyrimidine, no product at all was obtained when 3-methylpentane-2,4-dione[14] was employed in the same reaction. Acetylacetone and 2-mercapto-4-hydroxy-6-aminopyrimidine gave 2-mercapto-4-hydroxy-5,7-dimethylpyrido[2,3-d]pyrimidine in above 70% yield, but only a 7% yield was obtained when 3-methylpentane-2,4-dione was used, and when 3-ethyl[1] and 3-*n*-propyl[14] pentane-2,4-dione were employed the yields of 2-mercapto-4-hydroxy-5,7-dimethyl-6-ethylpyrido[2,3-d]pyrimidine and 2-mercapto-4-hydroxy-5,7-dimethyl-6-*n*-propylpyrido-[2,3-d]pyrimidine were 2.2 and 3.2%, respectively.

Alkyl substituted 3-ketoaldehydes, on the other hand, appeared to give better yields than the unsubstituted derivatives. Thus, although formylacetone[15] and 2,4,6-triaminopyrimidine gave 1% of the desired product, several experiments with other pyrimidines failed to yield any pyridopyrimidine. When the 2-methylbutan-3-one-1-al[16] was used, the yield of pyrido[2,3-d]pyrimidine increased to 35.4% in the reaction with 2-mercapto-4-hydroxy-6-aminopyrimidine. 2-Methylpentan-3-one-1-al[17] condensed with 2,4-diamino-6-hydroxypyrimidine to give 80.6% yield of 2-amino-4-hydroxy-6-methyl-7-ethylpyrido[2,3-d]-pyrimidine. Better yields were obtained when 2-methyl-3-phenylpropan-3-one-1-al[15] was used than when 3-phenylpropan-3-one-1-al[18] (formylacetophenone) was employed.

The possibility exists that superior product formation with the alkyl-substituted 3-ketoaldehydes is based on the greater stability of the substituted derivatives toward the acid medium required for condensation. Formylacetone is reported to give triacetylbenzene in acid solution[19] and formylacetophenone gives tribenzoylbenzene when heated in the presence of acetic acid.[20] This type of self-condensation to aromatic derivatives is blocked by the alkyl substitution. 2-Alkyl-3-ketoaldehydes are perhaps more stable than previously supposed since a number of these compounds could be distilled under reduced pressure without apparent decomposition.

On proceeding from symmetrical reagents, such as acetylacetone, to unsymmetrical dicarbonyl intermediates, such as formylacetone, an additional element of uncertainty was introduced, since the latter might condense to form either or both of two possible isomeric pyrido[2,3-d]pyrimidines depending on which of the carbonyl groups reacts with the pyrimidine 5-position. In order to establish the course of the reaction and the structures of the products, studies were undertaken to relate several of the pyrido[2,3-d]pyrimidines to the appropriate pyridines. To this end representatives of four series of pyridopyrimidines were synthesized by both routes.

The 7-phenylpyrido[2,3-d]pyrimidines were extensively investigated. Four derivatives (VII–X) were synthesized by the condensation of formylacetophenone with various 4-aminopyrimidines and these were then interrelated as shown in the reaction scheme.

The dihydroxy derivative X was synthesized, as shown, from 2-amino-6-phenylnicotinic acid, thus establishing the structures of all four derivatives. In similar experiments, formylacetone and formylcyclohexanone were condensed with 4-amino-2,6-dihydroxypyrimidine to give 2,4-dihydroxypyrido-[2,3-d]pyrimidines. Each of the latter also was prepared from the appropriate 2-aminonicotinic acid.

In each of these condensations of a ketoaldehyde with a 4-aminopyrimidine, only a single product

(13) A. Downow and P. Karlson, *Ber.*, **73**, 545 (1940).

(14) H. Adkins, W. Kutz and D. D. Coffman, THIS JOURNAL, **52**, 3219 (1930).

(15) L. Claisen and N. Stylos, *Ber.*, **21**, 1144 (1888).

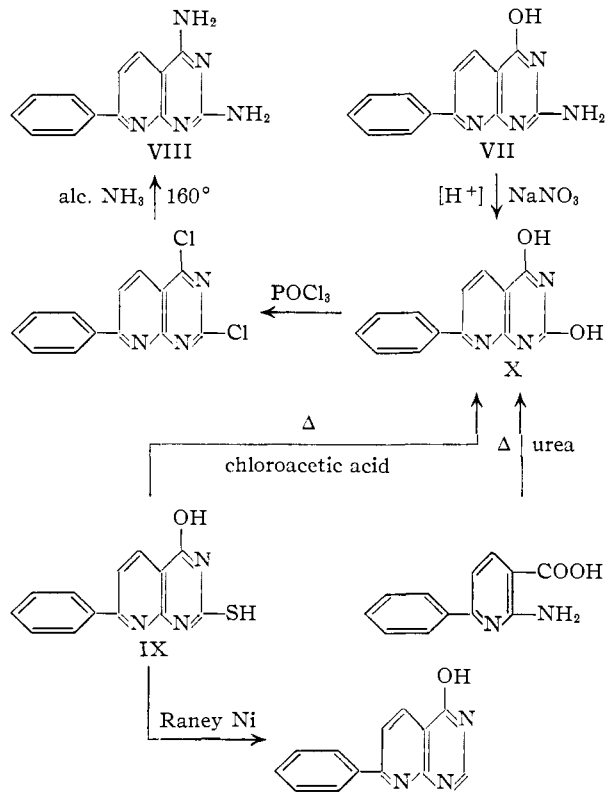
(16) A. H. Tracy and R. C. Elderfield, *J. Org. Chem.*, **6**, 66 (1941).

(17) L. Claisen and L. Meyerowitz, *Ber.*, **22**, 3276 (1889).

(18) C. Bulow and W. Suherer, *ibid.*, **34**, 3891 (1901).

(19) L. Claisen and N. Stylos, *ibid.*, **21**, 1145 (1888).

(20) L. Claisen, *Ann.*, **281**, 307 (1894).



could be detected, and it was the isomer formed by the reaction of the ketonic moiety with the 4-amino group of the pyrimidine and the aldehyde group with the 5-position of the pyrimidine ring. Nevertheless, it was clear that ketonic groups can condense with both positions as witnessed by the facile condensations of acetylacetone. Therefore, it was necessary to investigate the reaction through the use of an unsymmetrical diketone. Benzoylacetone condensed with 6-aminouracil to form a single product. This was identified as 2,4-dihydroxy-5-methyl-7-phenylpyrido[2,3-d]pyrimidine since the same product was obtained by the fusion with urea of 2-amino-4-methyl-6-phenylnicotinic acid.

Little can be said about the mechanism of this condensation at this time. Although it is possible to predict the allocation of substituents in most of the products, this has as yet little or no theoretical basis. However, the results suggest that condensation at the pyrimidine 5-position may occur initially, followed by cyclization. This finds an analogy in the condensation (under different conditions) of *o*-aminobenzaldehyde with similar pyrimidines to form pyrimido[4,5-b]quinolines.[21,22] Preliminary attempts to isolate an intermediate have failed.

In a number of instances condensations were repeated using concentrated sulfuric acid as a solvent with about the same results as when 85% phosphoric acid was used. A mixture of one-third polyphosphoric acid and two-thirds 85% phosphoric acid did increase the yield in several cases. This is believed to be due largely to the better solubility of some of the higher molecular weight 1,3-diketones and 3-ketoaldehydes in this solvent.

A number of 4-hydroxypyrido[2,3-d]pyrimidines was prepared by dethiolation of the 4-hydroxy-2-mercapto derivatives with Raney nickel (Table V). 4-Hydroxy-5,7-dimethylpyrido[2,3-d]pyrimidine was also prepared by heating 2-amino-4,6-dimethylnicotinic acid[13] with formamide. 4-Hydroxy-7-methylpyrido[2,3-d]pyrimidine, however, was prepared by heating 2-amino-6-methylnicotinic acid with formamide since the intermediate 2-mercapto-4-hydroxy-7-methylpyrido[2,3-d]pyrimidine could not be prepared from formylacetone and 2-mercapto-6-aminopyrimidine.

The ultraviolet absorption spectra of the pyrido[2,3-d]pyrimidines (Table VI) are in general primarily dependent on the nature of the substituent groups in the 2- and 4-position. The phenyl group and substituted phenyl group in position 7 usually cause some bathochromic shift. Alkyl groups in positions 5, 6 and 7 usually cause a smaller shift in the absorption maxima. However, with 2,4-diaminopyrido[2,3-d]pyrimidines an alkyl group in position 7 gives rise to a new absorption peak at *p*H of 1 at approximately 360 to 370 mμ. This peak is completely absent at *p*H 11.

In biological activities these substances closely resemble derivatives of related condensed pyrimidine systems. The diamino derivatives possess antifolic acid activity[23] of varying degrees and selectivity, which is manifest in antimalarial and antibacterial activities closely resembling those of the 2,4-diamino-6,7-dialkylpteridines.[24-28] Fuller descriptions of these activities will be presented elsewhere.

Experimental[29]

Melting points were determined in a copper block apparatus which was preheated to within 5–10° of the melting point.

Dicarbonyl Reagents.—The following dicarbonyl reagents were prepared as described in the literature: 3-methylpentane-2,4-dione,[14] 3-ethylpentane-2,4-dione,[14] 3-*n*-propylpentane-2,4-dione,[14] formylacetone,[15] 2-methylbutan-3-one-1-al,[16] 2-methylpentan-3-one-1-al,[17] 3-phenylpropan-3-one-1-al,[18] 2-methyl-3-phenylpropan-3-one-1-al[15] and formylcyclohexanone.[30]

Preparation of 3-Ketoaldehydes.—The 3-ketoaldehydes or their sodium salts employed in this investigation were prepared by formylation of the appropriate ketone with ethyl formate in the presence of sodium ethoxide in dry ether. Several did not separate from the ethereal solution as the sodium salts. These were extracted as the free ketoaldehydes and purified by distillation, although characterization was not attempted. These included the formyl derivatives of di-*n*-propyl, di-isobutyl, di-*n*-butyl and butyl ethyl ketone and butyrophenone. The method is illustrated for dipropyl ketone.

Formylation of Dipropyl Ketone.—Twenty grams of sodium was dissolved in 300 ml. of absolute ethanol and the

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(23) G. H. Hitchings, G. B. Elion and S. Singer, in "Chemistry and Biology of Pteridines," J. & A. Churchill Ltd., London, 1954, p. 272.
(24) L. J. Daniel, L. C. Norris, M. L. Scott and C. F. Heuser, *J. Biol. Chem.*, **169**, 689 (1947).
(25) G. H. Hitchings, G. B. Elion, H. Van der Werff and E. A. Falco, *ibid.*, **174**, 765 (1948).
(26) J. Greenberg, *J. Pharmacol.*, **97**, 484 (1949).
(27) H. O. J. Collier, N. R. Campbell and M. E. H. Fitzgerald, *Nature*, **165**, 1004 (1950).
(28) G. B. Elion and G. H. Hitchings, *J. Biol. Chem.*, **188**, 611 (1951).
(29) Melting points are uncorrected.
(30) P. A. Plattner, P. Treadwell and C. Scholz, *Helv. Chim. Acta*, **28**, 773 (1945).

solution was evaporated nearly to dryness under reduced pressure while being heated on the steam-bath. The flask was then cooled in an ice-bath and 100 ml. of dry ether added. A mixture of 100 g. of di-*n*-propyl ketone (0.88 mole) and 64.9 g. of ethyl formate (0.88 mole) was added dropwise with stirring; the reaction mixture was allowed to stand at room temperature overnight. The ethereal solution then was extracted with 400 ml. of cold water and the aqueous solution was re-extracted once with approximately 200 ml. of ether to remove any unreacted starting material. The aqueous solution was acidified with dilute acetic acid and the orange-colored oily layer removed by extraction with ether. This ethereal solution was washed with sodium bicarbonate solution to remove traces of excess acid, then dried over anhydrous magnesium sulfate. Evaporation of the ether left an orange oil which was distilled under reduced pressure to yield 100.4 g. of light yellow oil, b.p. 70–75° (15 mm.). The product appeared to be somewhat unstable, and was used within a few days of its preparation.

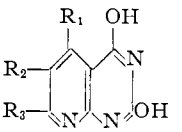
Preparation of Pyrido(2,3-d)pyrimidines from 4-Aminopyrimidines. General Method.—Equimolar proportions (usually 0.1 mole) of a 4-aminopyrimidine (substituted in the 2- and 6-positions with hydroxyl, amino or mercapto groups) and a 1,3-diketone or 3-ketoaldehyde are dissolved in 85% phosphoric acid (1.5 liters per mole). The reaction mixture is heated 3 to 5 hours on a steam-bath, then diluted with 4 to 5 volumes of water and cooled.

Precipitates are formed on standing by the 2,4-dihydroxy (Table I) and 2-mercapto-4-hydroxy derivatives (Table II). The 2-amino-4-hydroxy derivatives (Table IV) may precipitate as the phosphates or come down, as the free compounds, only after neutralization (usually with ammonium hydroxide). The 2,4-diamino derivatives (Table III) are soluble in dilute phosphoric acid and precipitate as the phosphates when the solution is neutralized.

The crude precipitates may be leached or digested with ethanol to remove tarry products and simplify further purification.

TABLE I

2,4-DIHYDROXYPYRIDO(2,3-d)PYRIMIDINE

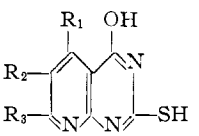


R_1	R_2	R_3	Empirical formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Yield, %	M.p., °C.	Solvent of crystn.
CH_3	H	CH_3	$C_9H_9N_3O_2$	56.5	56.6	4.70	4.66	22.0	22.1	58	304–305	HOAc
CH_3	H	C_6H_5	$C_{14}H_{11}N_3O_2$	66.5	66.4	4.38	4.45	16.6	16.3	17	308–310	HOAc
H	H	C_6H_5	$C_{13}H_9N_3O_2$	65.3	65.3	3.75	3.89	17.6	17.8	11	341–342	HOAc
H	CH_3	C_6H_5	$C_{14}H_{11}N_3O_2$	66.4	66.5	4.35	4.52	16.6	16.5	39	247–249	HOAc
H	C_2H_5	*n*-C_3H_7	$C_{12}H_{15}N_3O_2$	61.8	62.1	6.46	5.84	18.0	18.2	28	188–190	EtOH
H	H	$C_6H_5Cl(p)$	$C_{13}H_8N_3O_2Cl$	57.0	57.1	2.92	2.70	15.4	15.2	13	>360	HOAc
H	CH_3	*n*-C_4H_9	$C_{12}H_{15}N_3O_2$					18.0	18.0	22	209–211	H_2O–HOAc
H	C_6H_5	$CH_2C_6H_5$	$C_{20}H_{15}N_3O_2$	73.0	72.9	4.58	4.30	12.8	13.0	24[a]	248–249	HOAc
H	CH_3	C_2H_5	$C_{10}H_{11}N_3O_2$	58.5	58.8	5.36	5.33	20.3	20.4	28	218–220	EtOH
H	H	$C_6H_5CH_3(p)$	$C_{14}H_{11}N_3O_2$	66.4	66.2	4.35	4.74	16.6	16.6	14	>360	HOAc
H	H	$C_6H_5Br(p)$	$C_{13}H_8N_3O_2Br$	49.0	48.7	2.52	2.56	13.2	13.5	61	>360	HOAc
H	CH_3	CH_3	$C_9H_9N_3O_2$	56.5	56.7	4.70	4.58	22.0	21.7	29	329–330	HOAc
H	C_2H_5	C_6H_5	$C_{15}H_{13}N_3O_2$					15.75	15.75	26	231–233	EtOH

[a] This compound was prepared using mixture of one-third polyphosphoric acid and two-thirds 85% phosphoric acid in the condensation.

TABLE II

2-MERCAPTO-4-HYDROXYPYRIDO(2,3-d)PYRIMIDINES

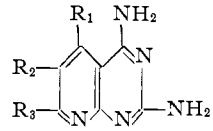


R_1	R_2	R_3	Empirical formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Yield, %	M.p., °C.	Solvent of crystn.
CH_3	H	CH_3	$C_9H_9N_3OS$	52.1	51.8	4.34	4.23	20.3	20.3	72	287–288	HOAc
H	$C_3H_7(i)$	$C_4H_9(i)$	$C_{11}H_{19}N_3OS$	60.5	60.1	6.94	6.56	15.1	14.9	14	208–209	EtOH
H	C_2H_5	*n*-C_3H_7	$C_{12}H_{15}N_3OS$	57.9	57.8	6.06	5.60	16.8	16.7	37	217–219	EtOH
H	CH_3	C_2H_5	$C_{10}H_{10}N_3OS$	54.5	54.5	4.55	4.70	19.1	19.2	45	238–240	EtOH
H	CH_3	C_6H_5	$C_{14}H_{11}N_3OS$	62.4	62.6	4.1	3.87	15.6	15.5	46	241–242	EtOH
H	C_6H_5	$CH_2C_6H_5$	$C_{20}H_{15}N_3OS$	69.6	69.6	4.38	4.59	12.1	11.9	21[a]	235–236	EtOH
H	CH_3	CH_3	$C_9H_9N_3OS$	52.1	52.7	4.54	3.95	20.3	20.7	35	300–302	HOAc
CH_3	CH_3	CH_3	$C_{10}H_{11}N_3OS$	54.3	54.2	4.98	4.46	19.1	19.3	7	305–307	EtOH
H	H	$C_6H_5Cl(p)$	$C_{13}H_8N_3OSCl$					14.5	14.4	13	335–337	HOAc
H	H	C_6H_5	$C_{13}H_9N_3OS$	61.2	61.2	3.53	3.43	16.5	16.6	26	310–312	HOAc
H	H	$C_{10}H_7(\alpha)$[a]	$C_{17}H_{11}N_3OS$	66.9	67.2	3.62	3.84	13.8	13.7	6	340–342	HOAc
CH_3	*n*-C_3H_7	CH_3	$C_{12}H_{15}N_3OS$	57.8	57.8	6.06	5.56	16.9	16.9	3	230–231	EtOH
CH_3	C_2H_5	CH_3	$C_{11}H_{13}N_3OS$	56.1	55.7	5.55	5.23			2	253–255	EtOH
H	C_2H_5	C_6H_5	$C_{15}H_{13}N_3OS$	63.7	63.9	4.63	4.82	14.9	14.9	49	212–213	EtOH
H	H	$C_6H_5Br(p)$	$C_{13}H_8N_3OSBr$	46.7	46.7	2.4	2.19	12.6	12.6	42	334–335	HOAc
H	CH_3	$C_4H_9(n)$	$C_{12}H_{15}N_3OS$	57.8	57.3	6.06	5.89	16.9	16.9	29	225–228	EtOH
H	H	$C_4H_9(i)$	$C_{11}H_{13}N_3OS$	56.2	56.5	5.57	5.60	17.8	17.6	29	210–211	EtOH–H_2O
H	H	$C_6H_5CH_3(p)$	$C_{14}H_{11}N_3OS$	62.4	62.3	4.10	4.07	15.6	15.8	29	219–220	HOAc

[a] A mixture of one-third polyphosphoric acid and two-thirds 85% phosphoric acid was used as the reaction medium.

TABLE III

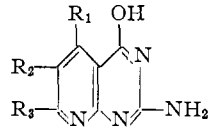
2,4-DIAMINOPYRIDO(2,3-d)PYRIMIDINES



R_1	R_2	R_3	Empirical formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Yield, %	M.p., °C.	Solvent of crystn.
CH_3	H	CH_3	$C_9H_{11}N_5$	57.1	56.8	5.87	5.93	37.0	37.4	3	305–306	EtOH
H	H	C_6H_5	$C_{13}H_{11}N_5$	65.9	66.3	4.68	5.0	29.5	29.2	25	289–290	EtOH–H_2O
H	CH_3	C_6H_5	$C_{14}H_{13}N_5$	66.9	67.1	5.2	5.33	27.8	27.6	10	287–290	EtOH–H_2O
C_6H_5	H	C_6H_5	$C_{19}H_{15}N_5$	72.9	72.9	4.80	4.58	22.4	22.8	1	288–290	EtOH
H	CH_3	C_2H_5	$C_{10}H_{13}N_5$	59.2	59.5	6.45	6.28	34.5	34.5	20	304–305	EtOH
H	H	CH_3	$C_8H_9N_5$					40.0	39.6	1	315 dec.	EtOH–H_2O
H	CH_3	CH_3	$C_9H_{11}N_5$	57.1	57.3	5.85	5.86	37.0	37.4	13	350–360 d.	EtOH–H_2O
H	H	$C_6H_4Cl(p)$	$C_{13}H_{10}N_5Cl$	57.6	58.0	3.69	3.53			11	311	EtOH
H	C_2H_5	C_6H_5	$C_{15}H_{15}N_5$	68.0	68.2	5.70	5.96	26.4	26.4	22	285–285	EtOH–H_2O
H	H	$C_6H_4Br(p)$	$C_{13}H_{10}N_5Br$	49.5	49.6	3.16	3.42	22.1	21.8	5	320	EtOH
H	C_2H_5	$C_6H_4Cl(p)$	$C_{15}H_{13}N_5Cl$	60.3	60.1	4.35	4.27	23.5	23.6	20	258–259	EtOH–H_2O
H	n-C_3H_7	C_6H_5	$C_{16}H_{17}N_5$	68.8	68.9	6.13	5.97	25.1	24.9	15	245–247	EtOH
H	CH_3	n-C_4H_9	$C_{12}H_{15}N_5$	63.0	62.7	6.58	6.97	30.5	30.2	8	275–278 d.	EtOH–H_2O
H	n-C_3H_7	n-C_4H_9	$C_{14}H_{21}N_5$					27.0	26.9	9	195–197	EtOH–H_2O
H	H	$C_6H_4CH_3$-(p)	$C_{14}H_{13}N_5$					27.9	28.0	5	323–325	EtOH
H	H	iso-C_4H_9	$C_{11}H_{15}N_5$	60.9	61.1	6.95	6.76	32.2	31.9	7	302–304	EtOH

TABLE IV

2-AMINO-4-HYDROXYPYRIDO(2,3-d)PYRIMIDINES



R_1	R_2	R_3	Empirical formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Yield, %	M.p., °C.
CH_3	H	CH_3	$C_9H_{10}N_4O$	56.7	56.4	5.32	5.22			43	>360
H	H	C_6H_5	$C_{13}H_{10}N_4O$	65.5	65.6	4.20	4.17	23.5	23.0	24	>360
H	CH_3	n-C_4H_9	$C_{12}H_{16}N_4O\cdot HCl$	53.6	53.4	6.33	6.49	20.8	20.6	29	225–230[a]
H	CH_3	C_6H_5	$C_{14}H_{12}N_4O\cdot HCl$	58.4	58.6	4.50	4.80	19.4	19.2	52	>360
H	CH_3	C_2H_5	$C_{10}H_{12}N_4O\cdot HCl$	49.9	50.0	5.40	5.27	23.2	22.8	81	335 dec.

[a] Placed in block at 200° and heated rapidly.

The phosphates of the diamino derivatives are converted to the free bases by digestion with an excess of warm dilute sodium hydroxide solution.

Some 2,4-dihydroxy and most 2-mercapto-4-hydroxy derivatives can be purified *via* the sodium salts. These are prepared by suspension of the crude precipitate in boiling water (2 to 3 liters per mole of reactants), addition of concentrated sodium hydroxide solution slowly until solution is effected, treatment with charcoal, filtration and cooling, whereupon the sodium salt usually crystallizes. The filtrate yields a second crop of crude material on acidification with acetic acid. The free compound is recovered from the sodium salt by solution in a minimal quantity of hot water and acidification with acetic acid.

Solution in hot dilute sodium hydroxide followed by acidification with acetic acid is a method of purification applicable to all derivatives except the diamino.

Several specific examples of the above methods are given below.

2,4-Dihydroxy-7-phenylpyrido(2,3-d)pyrimidine.—To 150 ml. of 85% phosphoric acid was added slowly with shaking 15.0 g. of 4-amino-2,6-dihydroxypyrimidine.[31] The mixture was warmed on the steam-bath to effect solution. After cooling to room temperature, 18.7 g. of the sodium salt of 3-phenylpropan-3-one-1-al[18] was added carefully. The reaction mixture was heated for 3 hours on the steam-bath and the contents poured into 500 ml. of water. The solution was filtered and the precipitate washed with water. It was suspended in 300 ml. of boiling ethanol, filtered and the product again digested in 300 ml. of hot ethanol. The compound was recrystallized from glacial acetic acid to give 3.2 g. of light yellow needles, m.p. 341–342°. A second recrystallization from the same solvent did not change the melting point.

4-Hydroxy-2-mercapto-5,7-dimethylpyrido(2,3-d)pyrimidine.—To 300 ml. of 85% phosphoric acid was added 35.8 g. of 6-amino-4-hydroxy-2-mercaptopyrimidine[32] in small portions with stirring. The mixture was heated to effect solution, then 25.0 g. of acetylacetone was added and heating was continued for 3.5 hr. on the steam-bath. The solution was added to 600 ml. of cold water, allowed to stand 20 minutes, and the precipitate was collected and washed with water. The precipitate was suspended in 300 ml. of boiling water and concentrated sodium hydroxide solution was added, a little at a time until all the product was in solution. Charcoal was added and the solution was filtered while hot. The filtrate, on cooling, deposited a voluminous precipitate of white needles. The mixture was filtered and washed with a little ice-water. This sodium salt was dissolved in hot water and the solution was acidified with acetic acid to yield 37.0 g. of white product, m.p. 285° (71.5% yield). A small amount was recrystallized from a large volume of ethanol to give an analytical sample, m.p. 287–288°.

2-Amino-4-hydroxy-6-methyl-7-ethylpyrido(2,3-d)pyrimidine.—Fifteen grams of 2,4-diamino-6-hydroxypyrimidine[33] was dissolved in 150 ml. of 85% phosphoric acid and the solution cooled while 14.6 g. of the sodium salt of 2-methylpentan-3-one-1-al[17] was added slowly. The mixture was heated for 5 hours on the steam-bath and then poured into 1 liter of cold water. The solution was neutralized with concentrated ammonium hydroxide and the resultant pre-

(31) J. Ruttink, *Rec. trav. chim.*, **65**, 764 (1946).

(32) W. Traube, *Ann.*, **331**, 71 (1904).

(33) *Org. Syntheses*, **32**, 45 (1952).

cipitate was removed by filtration. The crude precipitate was washed with water, suspended in 300 ml. of hot water and sufficient *N* sodium hydroxide was added to effect solution. The solution was warmed with a little charcoal, filtered and the hot filtrate acidified with dilute acetic acid. The filtered precipitate was washed repeatedly and then dried at 130° to give 19.5 g. of light tan amorphous product, m.p. 345–350°. 2-Amino-7-ethyl-4-hydroxy-6-methylpyrido(2,3-d)pyrimidine dissolves readily in strong mineral acids. A monohydrochloride was prepared by dissolving a small amount of the free base in hot ethanol which had previously been saturated with dry hydrogen chloride. The solution was allowed to cool overnight and the hydrochloride filtered and recrystallized from absolute ethanol.

2,4-Diamino-6-ethyl-7-phenylpyrido(2,3-d)pyrimidine.—2,4,6-Triaminopyrimidine[34] (31 g.) was dissolved in 250 ml. of 85% phosphoric acid, 44 g. of 2-ethyl-3-phenylpropan-3-one-1-al[17] was added and the solution was heated on the steam-bath for 4 hours. The reaction mixture was then poured into 1500 ml. of water and the solution stirred with charcoal and filtered. The clear filtrate was neutralized to *p*H 7 with concentrated ammonium hydroxide. The solid was collected and washed with water. This crude product was suspended in 200 ml. of hot water and the solution made strongly basic with sodium hydroxide and heated with occasional stirring on the steam-bath. After cooling, the light yellow product was filtered, washed with water and then recrystallized from an ethanol–water mixture which contained a little sodium hydroxide. The yield of colorless needles was 14.4 g., m.p. 282–283°. A small amount was recrystallized from absolute ethanol to give prisms, m.p. 283–285°.

Preparation of 4-Hydroxypyrido(2,3-d)pyrimidines (General Procedure).—From 5 to 10 g. of the appropriate 4-hydroxy-2-mercaptopyrido(2,3-d)pyrimidine was suspended in 1500–2000 ml. of ethanol; 100–200 ml. of concentrated ammonium hydroxide was added and the mixture was warmed on the steam-bath to effect solution. (Only in one or two instances was the starting material so insoluble that it could not be completely dissolved by this treatment before the addition of Raney nickel catalyst.) Then approximately 3 g. of wet Raney nickel catalyst W-5[35] was added for every gram of starting material and the reaction mixture was refluxed for 5 to 7 hours. The solution was filtered hot and the catalyst extracted once with 300 ml. of boiling ethanol. The combined filtrates were evaporated under reduced pressure to approximately 50 to 150 ml. and solution acidified with dilute acetic acid and allowed to cool. The substance was purified by recrystallization from ethanol–water unless otherwise stated.

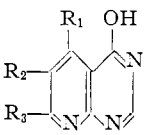
4-Hydroxy-6-methyl-7-phenylpyrido(2,3-d)pyrimidine.—Six grams of 2-mercapto-4-hydroxy-6-methyl-7-phenylpyrido(2,3-d)pyrimidine, m.p. 240–242°, was added to 1800 ml. of 95% ethanol and 150 ml. of concentrated ammonium hydroxide. After the addition of approximately 18–20 g. of Raney nickel catalyst the reaction mixture was refluxed for 6 hours on the steam-bath. The catalyst was then filtered off and extracted with 300 ml. of boiling 95% ethanol. The combined filtrates were evaporated under reduced pressure while heated by means of a steam-bath until the volume was about 100 ml. The hot solution was adjusted to *p*H 5 with dilute acetic acid and allowed to cool. The crude yield of white needles was 4.4 g., m.p. 245–248°. A second recrystallization from ethanol–water raised the m.p. to 248–250°.

(34) W. Traube, *Ber.*, **37**, 4545 (1904).

(35) "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 180.

TABLE V

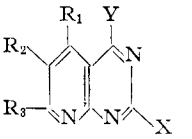
4-HYDROXYPYRIDO(2,3-d)PYRIMIDINES



R_1	R_2	R_3	Empirical formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Yield, %	M.p., °C.
CH_3	H	CH_3	$C_9H_9N_3O$	61.8	61.3	5.15	5.62	24.0	24.1	83	327–329
H	C_6H_5	$CH_2C_6H_5$	$C_{20}H_{15}N_3O$	76.7	77.1	4.83	5.04	13.4	13.5	68	239–240
H	CH_3	C_2H_5	$C_{10}H_{11}N_3O$	63.5	63.6	5.83	5.85	22.2	22.7	80	272–273
H	CH_3	CH_3	$C_9H_9N_3O$	61.8	62.1	5.16	5.03	24.0	23.9	69	>350 dec.
H	C_2H_5	*n*-C_3H_7	$C_{12}H_{15}N_3O$	66.4	66.7	6.96	6.89	19.4	19.7	80	224–225
H	CH_3	*n*-C_4H_9	$C_{12}H_{15}N_3O$	66.4	66.6	6.96	7.22	19.4	19.1	76	219–220
H	H	$C_6H_5Cl(p)$	$C_{13}H_8N_3OCl$	60.6	60.7	3.10	3.43	16.3	16.3	64	348–349
H	H	*iso*-C_4H_9	$C_{11}H_{13}N_3O$	65.0	64.8	6.4	6.10	20.7	20.4	66	248–250
H	CH_3	C_6H_5	$C_{14}H_{11}N_3O$	71.0	71.2	4.65	4.95	17.7	17.7	84	248–250
H	H	C_6H_5	$C_{13}H_9N_3O$	70.0	70.1	4.04	4.16	18.8	18.7	44	260–263
H	H	$C_6H_5CH_3(p)$	$C_{14}H_{11}N_3O$	71.0	70.9	4.65	4.48	17.7	17.5	74	312–315
H	C_2H_5	C_6H_5	$C_{15}H_{13}N_3O$	71.8	71.8	5.19	5.12	16.7	16.6	58	224–226

TABLE VI

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



(i) = inflection.

R_1	R_2	R_3	*p*H 1.0 λ_{max}, mμ	*p*H 1.0 $E_m \times 10^{-3}$	*p*H 1.0 λ_{min}, mμ	*p*H 1.0 $E_m \times 10^{-3}$	*p*H 10.7 λ_{max}, mμ	*p*H 10.7 $E_m \times 10^{-3}$	*p*H 10.7 λ_{min}, mμ	*p*H 10.7 $E_m \times 10^{-3}$
			X = Y = NH_2							
H	H	CH_3	313	8.9	345	1.7	265	5.9	260	5.7
			362	2.2			338	7.1	290	1.0
CH_3	H	CH_3	313	7.5	293	4.1	265(i)	(7)	290	1.4
			356	3.9	340	3.2	337	7.3		
H	C_2H_5	$C_3H_7(n)$	325	9.8	297	3.5	265(i)	(9)	292	1.0
			373	3.7	353	3.5	345	9.4		

CH_3	CH_3	CH_3	280	7.3	270	6.5	265(i)	(9)	293	1.6
			330	7.1	297	2.8	342	8.3		
			362	5.2	348	4.5				
H	H	C_6H_5	245(i)	(15)	298	5.1	240	22.1	245	20.2
			337	21.5			260	25.8	310	3.2
							350	12.7		
H	CH_3	C_6H_5	335	14.8	298	3.9	251	23.8	240	22.1
							355	10.2	300	2.1
C_6H_5	H	C_6H_5	343	19.6	310	6.7	265	29.8	320	2.7
							365	10.5		
				X = NH_2, Y = OH						
CH_3	H	CH_3	275	11.0	250	3.8	268	6.6	258	6.0
			335	9.5	292	2.0	324	6.2	288	2.0
H	H	C_6H_5	275	10.0	262	7.9	234	19.0	242	18.0
			328	12.6	296	5.1	256	21.8	301	3.2
			368	6.2	358	5.4	343	8.2		
H	CH_3	C_2H_5	276	12.0	250	6.0	268	8.4	256	7.0
			348	8.4	298	2.8	333	6.4	293	2.5
H	CH_3	C_6H_5	278	15.7	250	9.0	248	23.4	292	1.9
			367	13.1	298	2.6	345	7.8		
				X = Y = OH						
H	H	CH_3	307	9.2	265	0.9	265	5.9	253	4.5
							309	7.3	280	2.0
CH_3	H	CH_3	307	11.6	265	1.2	266	8.7	255	5.7
							310	7.2	280	3.0
H	C_2H_5	$C_3H_7(n)$	248	7.1	235	6.2	265	8.3	255	7.0
			318	11.3	272	0.5	320	8.5	285	2.0
H	H	C_6H_5	240	12.7	240	11.7	263	15.9	245	15.0
			265	10.5	260	10.0	333	14.6	300	4.2
			327	20.0	289	4.9				
H	CH_3	C_6H_5	247	12.4	240	11.3	265(i)		290	2.4
			327	14.2	283	2.5	330	11.0		
CH_3	H	C_6H_5	270	10.5	260	9.0	260	18.1	246	17.3
			325	13.9	325	13.9	330	11.7	297	4.1
H	C_6H_5	$C_6H_5CH_2$	255	15.5	241	12.3	274	14.5	258	12.5
			320	9.2	288	3.0	325	8.2	300	4.4
				X = SH, Y = OH						
CH_3	H	CH_3	282	22.2	245	8.6	297	21.8	265	9.3
			311	14.2	300	13.4				
H	C_2H_5	$C_3H_7(n)$	288	18.7	248	4.2	238	13.1	257	7.0
			330	10.3	306	7.0	300	21.9	335(i)	
CH_3	CH_3	CH_3	284	23.1	245	6.2	260	10.2	260	10.2
			325	12.0	305	9.6	300	22.8		
H	H	C_6H_5	285	26.6	312	8.0	240	17.5	246	16.8
			345	17.5			298	26.2	327	8.2
							351	10.7		
H	CH_3	C_6H_5	287	28.8	245	7.5	300	25.3	245	12.2
			340	13.7	310	7.0	348	9.7	310	7.0
H	C_6H_5	$C_6H_5CH_2$	292	20.6	255	10.0	308	27.6	261	9.8
			335(i)							
				X = H, Y = OH						
H	H	CH_3	280(i)	(3.6)	247	1.6	318	11.2	255	2.6
			318	11.2						
CH_3	H	CH_3	313	13.0	247	1.8	308	8.9	255	2.5
H	C_2H_5	$C_3H_7(n)$	272	5.0	252	2.7	280	4.3	257	3.1
			323	13.6	290	2.9	316	9.6	288	3.7
H	H	C_6H_5	244	16.3	292	5.7	255	25.9	297	6.5
			332	18.3			328	14.9		
H	CH_3	C_6H_5	265	7.3	255	6.7	243	17.8	292	3.2
			338	16.7	293	3.2	326	11.6		

2,4-Dihydroxy-7-methylpyrido(2,3-d)pyrimidine.—Twenty grams of 2-amino-6-methylnicotinic acid[13] was fused with 45 g. of urea as described earlier for 2-aminonicotinic acid.[8] The temperature of the melt was maintained at 180–200° for 10 minutes and gradually raised to 220° over a period of 15 minutes. The solid was dissolved in 350 ml. of hot 4 *N* sodium hydroxide, treated with charcoal and filtered. The hot filtrate was saturated with carbon dioxide, and allowed to cool, yielding 14.6 g. of crude product. Three grams of this material was recrystallized from glacial acetic acid to give 2.7 g., m.p. 314–315°.

Anal. Calcd. for $C_8H_7N_3O_2$: C, 54.3; H, 3.95; N, 23.7. Found: C, 54.3; H, 3.90; N, 23.3.

2,4-Dichloro-7-methylpyrido(2,3-d)pyrimidine.—To 250 ml. of phosphorus oxychloride was added 10.0 g. of 2,4-dihydroxy-7-methylpyrido(2,3-d)pyrimidine. The solution was refluxed for 2.5 hours after which time the solution had turned a dark reddish-purple. The excess phosphorus oxychloride was removed under reduced pressure and the sirupy residue was poured onto ice and allowed to stand for 10 to 15 minutes. The solution was then extracted with chloroform and the chloroform extracts washed and dried over magnesium sulfate. Evaporation of the chloroform solution gave 1.7 g. of crude purple product, m.p. 160–165°. A small amount was recrystallized from *n*-heptane to yield orange plates, m.p. 165–169°.

Anal. Calcd. for $C_8H_5N_3Cl_2$: C, 44.8; H, 2.34; N, 19.6. Found: C, 45.1; H, 2.34; N, 19.9.

2,4-Diamino-7-methylpyrido(2,3-d)pyrimidine.—To 20 ml. of alcoholic ammonia (saturated at 0°) was added 1.2 g. of crude 2,4-dichloro-7-methylpyrido(2,3-d)pyrimidine, and the solution was heated in a bomb at 155° overnight. The solution was then evaporated to dryness on the steam-bath, 30 ml. of 2 *N* sodium hydroxide was added and solution cooled overnight in the refrigerator. The red needles were filtered, washed and recrystallized from aqueous ethanol to yield 0.5 g. of light pink product, m.p. 315° dec.

Anal. Calcd. for $C_8H_9N_5$: N, 40.0. Found: N, 39.5.

This product was found to be identical with the product obtained by the reaction of formylacetone and 2,4,6-triaminopyrimidine in 85% phosphoric acid.

2,4-Dihydroxy-5,7-dimethylpyrido(2,3-d)pyrimidine. Method 1.—2-Amino-4,6-dimethylnicotinic acid,[13] m.p. 258–259°, 9.0 g., and 18.0 g. of urea were heated together as described above for 2,4-dihydroxy-7-methylpyrido(2,3-d)-pyrimidine. The crude product was recrystallized twice from glacial acetic acid and dried at 140° to give 3.6 g. of colorless needles, m.p. 304–306°, unchanged by admixture with the product of the reaction of acetylacetone with 2,4-dihydroxy-6-aminopyrimidine. Ultraviolet absorption spectra of the two preparations were identical.

Method 2.—To a solution of 2.5 g. of chloroacetic acid in 15 ml. of water was added 2.5 g. of 2-mercapto-4-hydroxy-5,7-dimethylpyrido(2,3-d)pyrimidine prepared by the condensation of acetylacetone and 2-mercapto-4-hydroxy-6-aminopyrimidine. The solution was evaporated to dryness on the steam-bath. The residue was dissolved in 10 *N* hydrochloric acid (10 ml.) and the solution was refluxed for 3 hours and diluted to 500 ml. The solution was neutralized by the addition of concentrated ammonium hydroxide (*p*H 7). The crude precipitate was recrystallized from glacial acetic acid to yield 1.4 g. of white crystals, m.p. 304–306° unchanged by admixture with the product of method 1 above. Ultraviolet absorption spectra of the two products were identical.

2,4-Dichloro-5,7-dimethylpyrido(2,3-d)pyrimidine.—Five grams of 2,4-dihydroxy-5,7-dimethylpyrido(2,3-d)pyrimidine was heated at reflux temperature with phosphorus oxychloride for 2.5 hours, and worked up as in the preparation of 2,4-dichloro-7-methylpyrido(2,3-d)pyrimidine. The yield of pink product recrystallized from *n*-heptane was 0.6 g., m.p. 154–155°.

Anal. Calcd. for $C_9H_7N_3Cl_2$: C, 47.4; H, 3.07; N, 18.4. Found: C, 47.4; H, 2.75; N, 18.5.

2,4-Diamino-5,7-dimethylpyrido(2,3-d)pyrimidine.—Four-tenths grams of 2,4-dichloro-5,7-dimethylpyrido(2,3-d)pyrimidine, m.p. 154–155°, was treated with alcoholic ammonia at 155° as in the preparation of 2,4-diamino-7-methylpyrido(2,3-d)pyrimidine to give 0.3 g. of colorless needles, m.p. 305–306°, unchanged on admixture with the product prepared by the reaction of acetylacetone and 2,4,6-triaminopyrimidine in 85% phosphoric acid. The two products were found to have identical ultraviolet absorption spectra.

2,4-Dihydroxy-6,7-dimethylpyrido(2,3-d)pyrimidine. Method 1.—Three grams of 2-amino-5,6-dimethylnicotinic acid[36] was fused with 9 g. of urea and the product isolated in a manner similar to that described for 2,4-dihydroxy-7-methylpyrido(2,3-d)pyrimidine. Recrystallization of the crude product from glacial acetic acid gave 1.1 g. of light yellow needles which were dried at 140°, m.p. 329–330°, unchanged when mixed with 2,4-dihydroxy-6,7-dimethylpyrido(2,3-d)pyrimidine prepared by the condensation of 2,4-dihydroxy-6-aminopyrimidine and 2-methylbutan-3-one-1-al[16] in 85% phosphoric acid. The ultraviolet absorption spectra of the two products were identical.

Method 2.—One gram of 2-mercapto-4-hydroxy-6,7-dimethylpyrido(2,3-d)pyrimidine (prepared by the condensation of 2-mercapto-4-hydroxy-6-aminopyrimidine with 2-methylbutan-3-one-1-al) was treated with chloroacetic acid as described above for the 5,7-dimethyl isomer. The product was recrystallized from glacial acetic acid to give 0.5 g., m.p. 329–330°. This product was identical with that prepared by method 1 as evidenced by mixed melting point and ultraviolet absorption spectrum.

2,4-Diamino-6,7-dimethylpyrido(2,3-d)pyrimidine.—Two grams of 2,4-dihydroxy-6,7-dimethylpyrido(2,3-d)pyrimidine was chlorinated with phosphorus oxychloride as in the preparation of 2,4-dichloro-7-methylpyrido(2,3-d)pyrimidine. The crude dichloro derivative was then treated with alcoholic ammonia at 155–160° to yield 1.0 g. of crude product; after recrystallization from ethanol–water there was obtained 0.8 g. of light orange needles, m.p. 350–360° dec. A mixture of this product and that prepared by the condensation of 2,4,6-triaminopyrimidine and 2-methylbutan-3-one-1-al melted similarly, 350–360° dec. The ultraviolet absorption spectra of the two compounds were identical.

2,4-Dihydroxy-7-phenylpyrido(2,3-d)pyrimidine. Method 1.—Two hundred milligrams of 2-amino-6-phenylnicotinic acid,[36] m.p. 240°, was heated with 1.0 g. of urea at 180–200° for 15 minutes. The cooled melt was dissolved in 2 *N* sodium hydroxide and the solution acidified with acetic acid. The crude product was recrystallized twice from glacial acetic acid to yield 40 mg. of white needles, m.p. 340–341°, unchanged on admixture with the same compound prepared by condensation of 2,4-dihydroxy-6-aminopyrimidine and 3-phenylpropan-3-one-1-al. Ultraviolet absorption spectra showed the compounds to be identical.

Method 2.—One gram of 2-mercapto-4-hydroxy-7-phenylpyrido(2,3-d)pyrimidine was added to a solution of 15 g. of chloroacetic acid and 10 g. of water and the solution was evaporated to dryness on the steam-bath. The residue was dissolved in 75 ml. of 10 *N* hydrochloric acid, and the solution was refluxed for 3 hours, diluted to 500 ml. and neutralized with concentrated ammonium hydroxide (*p*H 7). The mixture was then filtered, and the solid was washed and recrystallized from glacial acetic acid to give 0.5 g. of colorless needles, m.p. 341–342°. Mixed melting point data and ultraviolet absorption spectra showed the compound to be identical with that prepared by method 1.

Method 3.—One gram of 2-amino-4-hydroxy-7-phenylpyrido(2,3-d)pyrimidine (from 2,4-diamino-6-hydroxypyrimidine and formylacetophenone) was dissolved in 500 ml. of boiling 5 *N* sulfuric acid. To the hot solution was carefully added a solution of 3.6 g. of sodium nitrite dissolved in 10 ml. of water. The solution was reheated to boiling and then allowed to cool gradually while standing overnight. The solution was filtered from what proved to be a mixture of the sulfate of the starting material and some 2,4-dihydroxy-7-phenylpyrido(2,3-d)pyrimidine. The filtrate was made neutral with ammonium hydroxide and the resulting precipitate was removed by filtration. The crude product was recrystallized from glacial acetic acid to give 0.2 g. of white crystals, m.p. 334–338°. A second recrystallization from the same solvent raised the m.p. to 339–341°. This product showed no depression in melting point when mixed with 2,4-dihydroxy-7-phenylpyrido(2,3-d)pyrimidine prepared by methods 1 and 2, and the ultraviolet absorption spectrum was identical to that of the products of method 1 and method 2.

2,4-Dichloro-7-phenylpyrido(2,3-d)pyrimidine.—To 150 ml. of phosphorus oxychloride was added 4.5 g. of 2,4-dihy-

(36) A. Dornow and E. Neuse, *Ber.*, **84**, 300 (1951).

droxy-7-phenylpyrido(2,3-d)pyrimidine. The reaction mixture was refluxed for 24 hours, after which time all the starting material had apparently dissolved. The excess phosphorus oxychloride was removed under reduced pressure and the sirupy residue was poured over crushed ice. The aqueous suspension was then extracted with chloroform and the chloroform extracts washed and dried over anhydrous magnesium sulfate. Evaporation of the chloroform left 5.1 g. of a white product, m.p. 200–205°. A small amount was recrystallized from heptane (Skellysolve C) to raise the m.p. to 204–206°.

Anal. Calcd. for $C_{13}H_{17}N_3Cl_2$: N, 15.2. Found: N, 15.1.

2,4-Diamino-7-phenylpyrido(2,3-d)pyrimidine.—To 25 ml. of alcoholic ammonia (absolute ethanol saturated with dry ammonia at 0°) was added 1.5 g. of 2,4-dichloro-7-phenylpyrido(2,3-d)pyrimidine, m.p. 200–205°, and the solution was heated in a bomb at 155° for 15 hours. The bomb contents were evaporated to 10 ml., the residue was extracted with dilute sodium hydroxide solution and then recrystallized from aqueous ethanol to give 0.9 g. of light green needles, m.p. 289–290°. A mixed melting point with 2,4-diamino-7-phenylpyrido(2,3-d)pyrimidine prepared by the condensation of 2,4,6-triaminopyrimidine and 3-phenylpropan-3-one-1-al was 289–290°. Ultraviolet absorption spectra of the two compounds were identical.

2-Mercapto-4-hydroxy-6,7,8,9-tetrahydropyrimido(4,5-b)quinoline.—Ten grams of 2-mercapto-4-hydroxy-6-aminopyrimidine was dissolved in 100 ml. of 85% phosphoric acid and the solution cooled while 11.4 g. of the sodium salt of formylcyclohexanone[30] was added carefully. The solution was heated 2 hours on the steam-bath and then was poured into 800 ml. of cold water. The crude product was dissolved in hot 2 *N* sodium hydroxide, treated with carbon and the filtrate was acidified with acetic acid while still hot. After two recrystallizations from glacial acetic acid there was obtained 6.2 g. of light green needles, m.p. 252–255°.

Anal. Calcd. for $C_{11}H_{11}N_3OS$: C, 56.6; H, 4.72; N, 18.0. Found: C, 56.9; H, 4.69; N, 18.2.

2,4-Dihydroxy-6,7,8,9-tetrahydropyrimido(4,5-b)quinoline. Method 1.—Forty-four grams of 2,6-dihydroxy-4-aminopyrimidine[16] was dissolved in 400 ml. of 85% phosphoric acid and 52.0 g. of the sodium salt of formylcyclohexanone[30] was added slowly and the reaction mixture heated 5 hours on the steam-bath. The solution was then poured into 1500 ml. of water and allowed to stand. The crude product was dissolved in dilute sodium hydroxide, treated with carbon and the filtrate was acidified with acetic acid. The crude product was recrystallized from 95% acetic acid to give 21.0 g. of tan needles, m.p. 304–306°. A second recrystallization from glacial acetic acid raised the m.p. to 306–308°.

Anal. Calcd. for $C_{11}H_{11}N_3O_2$: C, 60.8; H, 5.08; N, 19.4. Found: C, 60.8; H, 5.16; N, 19.1, 19.7.

Method 2.—Three grams of 2-amino-5,6,7,8-tetrahydroquinoline-3-carboxylic acid,[38] m.p. 292°, prepared from the amide, was heated with 8 g. of urea at 180–200° until the solution became thick and mushy. The cooled melt was dissolved in hot dilute sodium hydroxide, then acidified with acetic acid while hot. The product was recrystallized from 95% acetic acid to give 1.4 g., m.p. 304–306°. A second recrystallization from the same solvent raised the m.p. to 306–308°. A mixture with 2,4-dihydroxy-6,7,8,9-tetrahydropyrimido(4,5-b)quinoline prepared by method 1 melted at 306–308°. The ultraviolet absorption spectra of the products prepared by method 1 and method 2 were identical.

Method 3.—One gram of 2-mercapto-4-hydroxy-6,7,8,9-tetrahydropyrimido(4,5-b)quinoline was added to 15 g. of chloroacetic acid in 10 ml. of water and the solution was evaporated to dryness on the steam-bath. The residue was refluxed with 25 ml. of 10 *N* hydrochloric acid for 3 hours, diluted to 500 ml. and neutralized with ammonium hydroxide (*p*H 7). The crude product was filtered and recrystallized from glacial acetic acid to give 0.3 g. of needles, m.p. 305–308°. This material did not depress the m.p. of the same compound prepared by method 1 or method 2. Ultraviolet absorption spectral data confirmed the identity of the products.

2,4-Dihydroxy-5-methyl-7-phenylpyrido(2,3-d)pyrimidine.—One gram of 2-amino-4-methyl-6-phenylnicotinic acid,[38] m.p. 265°, prepared from the ester was fused with 4 g. of urea. After extraction with base and acidification with acetic acid, 0.5 g. of crude product was obtained. Recrystallization from glacial acetic acid gave colorless needles which melted at 308–310°. A mixed melting point of this product and the product of the condensation of benzoylacetone with 2,4-dihydroxy-6-aminopyrimidine was 308–310°. Ultraviolet absorption spectra of the two preparations were identical.

4-Hydroxy-5,7-dimethylpyrido(2,3-d)pyrimidine.—Six grams of 2-amino-4,6-dimethylnicotinic acid[38] and 12 g. of formamide were heated at 160–165° (internal temperature) for 1.5 hours. The solution was cooled, added to 50 ml. of water and allowed to stand. The crude brown product was dissolved in hot 50% ethanol and treated with charcoal. The yield of almost colorless needles was 3.2 g., m.p. 324–327°. A second recrystallization from the same solvent raised the melting point to 327–329°. A mixed melting point of this substance with the product of dethiolation of 2-mercapto-4-hydroxy-5,7-dimethylpyrido(2,3-d)pyrimidine was 327–329°. The ultraviolet absorption spectra of the two compounds were identical.

4-Hydroxy-7-methylpyrido(2,3-d)pyrimidine.—Six grams of 2-amino-6-methylnicotinic acid and 12 g. of formamide were heated for 2.5 hours at 170–180° (internal temperature). The cooled solid was treated as described in the previous preparation, recrystallized from ethanol–water and then from water to yield 3.4 g. of slightly yellow needles, m.p. 309–311°.

Anal. Calcd. for $C_8H_7N_3O$: C, 59.7; H, 4.35; N, 26.0. Found: C, 59.3; H, 3.87; N, 25.9.

2,4-Dihydroxypyrimido(2,3-d)pyrimidine.—6-Aminouracil[31] (10 g.) was dissolved in a mixture of 85% phosphoric acid (70 ml.) and polyphosphoric acid (40 ml.) by warming, and malondialdehyde diacetal (a commercial trimethylmonoethyl derivative) (20 ml.) was added. The mixture was heated on the steam-bath for 4.5 hours, meanwhile turning dark red in color. After the addition of 500 ml. of water the solution was allowed to stand overnight at 5°. The precipitate was removed by filtration, suspended in 500 ml. of hot water and dissolved by the addition of 40 ml. of 2 *N* sodium hydroxide. After treatment with carbon and filtration, the product was reprecipitated by the addition of 10 ml. of acetic acid to the hot solution. The precipitate was recovered by filtration, washed with acetone (which removes some brown material) and air-dried. At this point it weighed 9 g., an apparent 70% yield, but the substance was only about 70% pure by spectrographic analysis.

Recrystallization from 6 *N* acetic acid gave an excellent return of analytically pure material, identical in every respect with the 2,4-dihydroxypyrido(2,3-d)pyrimidine prepared earlier from 2-aminonicotinamide.[8]

Anal. Calcd. for $C_7H_5N_3O_2$: C, 51.5; H, 3.1; N, 24.5. Found: C, 51.3; H, 2.5; N, 24.3.

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