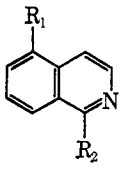
TABLE II



Compd	R_1	R_2	Recrystn solvent	Yield, %	Mp, °C	Formula	Analyses
II[a]	NO_2	CH_3	EtOH	70	150–151	$C_{10}H_8N_2O_2$	N
III[b]	NO_2	CHO	50% EtOH	50	175–176	$C_{10}H_6N_2O_3$	
VI[a]	NH_2	CH_3	C_6H_6	92	213–214	$C_{10}H_{10}N_2$	N
VII[a]	$NHCOCH_3$	CH_3	Dioxane	90	226–227	$C_{12}H_{12}N_2O$	C, H, N
VIII[b]	$NHCOCH_3$	CHO	C_6H_6	75	206–207	$C_{12}H_{10}N_2O_2$	C, H, N
XV[a]	$OCOCH_3$	CH_3	Hexane	94	99–100	$C_{12}H_{11}NO_2$	C, H, N
XVI[b]	$OCOCH_3$	CHO	Hexane	70	100–101	$C_{12}H_9NO_3$	C, H, N

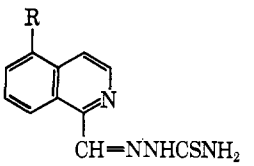
[a] Compounds were synthesized utilizing standard procedures and reactants as described in the Chemistry section. [b] The general procedure used for the oxidation reactions is given in the Experimental Section.

ml of H_2O, and filtered, and the filtrate was made acidic with 10% HCl. The undissolved material was removed by filtration using Celite and the filtrate was made alkaline with $NaHCO_3$. The precipitate of XIV was filtered, washed (H_2O), and dried to give a light brown product; yield 2.4 g (75%). Crystallization from EtOH after treatment with Norit A gave white crystals, which collapsed at 268–270° and finally melted at 295–300° dec. *Anal.* ($C_{10}H_9NO$) N.

1-Formylisoquinoline-5-sulfonic Acid Thiosemicarbazone (XII). —Compound XI[4] (1.15 g, 0.005 mole) was mixed slowly in small portions with 20 g of fuming (30%) H_2SO_4 at 0°. Addition of the compound required 15 min to ensure the maintenance of temperature at 0°. The solution was stirred for 2 hr and then kept at room temperature for 18 hr. The mixture was then decomposed in 100 g of ice flakes; the red precipitate was filtered, washed (cold H_2O), and dissolved in a 5% solution of $NaHCO_3$. The resulting yellow solution was filtered to remove insoluble material and the filtrate was made acidic (dilute AcOH). The resulting precipitate was collected by filtration, washed (H_2O, EtOH), and then dried to give 1.2 g (78%). *Anal.* ($C_{11}H_{10}N_4O_3S_2$) C, H, N, S.

Thiosemicarbazones.—The thiosemicarbazones V, IX, XVII, and XXI were prepared by treating alcoholic solutions of the corresponding aldehydes with an aqueous solution of thiosemicarbazide acidified with a few drops of dilute AcOH. Relevant data concerning these compounds are listed in Table III. Compound XIX was best obtained by directly treating the acid-hydrolyzed solution of VIII with a solution of thiosemicarbazide followed by neutralization (NaOAc).

TABLE III



Compd	R	Mp, °C dec	Formula	Analyses
V	NO_2	238–240	$C_{11}H_9N_5O_2S$	C, H, N, S
IX	$NHCOCH_3$	230–232	$C_{13}H_{13}N_5OS \cdot H_2O$	H, N, S; C[a]
XVII	$OCOCH_3$	200–201	$C_{13}H_{12}N_4O_2S$	C, H, N, S
XIX	NH_2	223–225	$C_{11}H_{11}N_5S$	C, H, N, S
XXI	OH	224–226	$C_{11}H_{10}N_4OS$	C, H, N, S

[a] C: calcd, 51.15; found, 51.73.

Studies on Condensed Pyrimidine Systems. XXIII. Synthesis of 2,4-Diaminopyrido[2,3-*d*]pyrimidines from β-Keto Esters[1]

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The condensation of 2,4,6-triaminopyrimidine with β-keto esters gave 5-mono- and 5,6-disubstituted 2,4-diamino-7,8-dihydro-7-oxopyrido[2,3-*d*]pyrimidines (III) which were chlorinated by means of thionyl chloride and N,N-dimethylformamide to give 7-chloro-2,4-diaminopyrido[2,3-*d*]pyrimidines (V). Both the 7-oxo and 7-chloro derivatives were thiated to give 2,4-diaminopyrido[2,3-*d*]pyrimidine-7-thiones (IV). Dethiation of the 7-thiones gave 2,4-diaminopyrido[2,3-*d*]pyrimidines having substituents in the 5 or 5,6 positions.

The study[2-6] in this laboratory of pyrimidine and condensed pyrimidine systems as inhibitors of dihydrofolate reductase led to an investigation of 2,4-diaminopyrido[2,3-*d*]pyrimidines. In 1958, Robins and Hitchings[2] reported the synthesis of a number of pyrido[2,3-*d*]pyrimidines. The 2,4-diamino compounds (Ia) have been found to be inhibitors of dihydrofolate reductase. However, only pyrido[2,3-*d*]pyrimidines having alkyl or aryl substituents in the 7 position were prepared. 5,6-Disubstituted derivatives (II) were expected to exhibit greater enzyme binding because they more closely resemble the natural substrate in configuration.

The key intermediates, 5,6-disubstituted 2,4-diamino-7,8-dihydro-7-oxopyrido[2,3-*d*]pyrimidines (III), were prepared by heating a mixture of a β-keto ester and 2,4,6-triaminopyrimidine to a temperature above 200° either alone or in an inert solvent such as diphenyl

(1) The previous paper in this series was by G. B. Elion, *J. Org. Chem.*, **27**, 2478 (1962).

(2) R. K. Robins and G. H. Hitchings, *J. Am. Chem. Soc.*, **80**, 3449 (1958).

(3) R. K. Robins and G. H. Hitchings, *ibid.*, **77**, 2256 (1955).

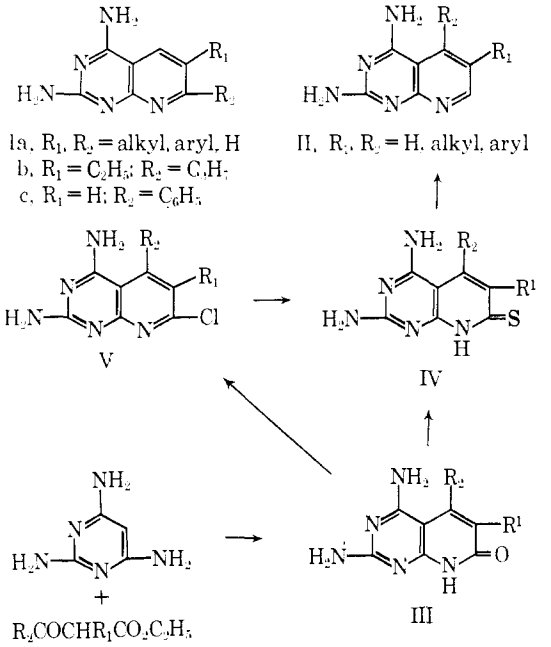
(4) G. H. Hitchings and K. W. Ledig, U. S. Patent 2,937,284 (1960).

(5) G. H. Hitchings, T. A. Herrmann, B. S. Hurlbert, and S. R. M. Bushby, Proceedings of the IIIrd International Congress of Chemotherapy, Stuttgart, 1963, p 1363.

(6) G. H. Hitchings and J. J. Burchall, *Advan. Enzymol.*, **27**, 417 (1965).

ether (see Scheme I). The analytical values for each product showed it to be a 1:1 condensation product produced by the loss of one molecule each of ethanol and water from the combined reactants.

SCHEME I



There are six possible isomeric structures for such a condensation product: 2,4-diamino-5,8-dihydro-5-oxopyrido[2,3-*d*]pyrimidine (VI), 2,4-diamino-7,8-dihydro-7-oxopyrido[2,3-*d*]pyrimidine (III), 6,8-diamino-2-oxo-2H-pyrimido[1,2-*c*]pyrimidine (VII), 6,8-diamino-4-oxo-4H-pyrimido[1,2-*c*]pyrimidine (VIII), 6,8-diamino-2-oxo-2H-pyrimido[1,2-*a*]pyrimidine (IX), and 6,8-diamino-4-oxo-4H-pyrimido[1,2-*a*]pyrimidine (X). The proof that structure III is correct for the condensation product obtained depended upon the reduction of the oxo compounds to 7-unsubstituted 2,4-diaminopyrido-[2,3-*d*]pyrimidines. This reduction was accomplished *via* the 2,4-diamino-7,8-dihydropyrido[2,3-*d*]pyrimidine-7-thiones (IV). The latter were prepared directly from the oxo compounds and also *via* the corresponding 7-chloro derivatives (V).

The oxo compounds (III) could be chlorinated to give V with thionyl chloride in *N*,*N*-dimethylformamide (DMF) and chloroform, a modification of a method reported[7] for the chlorination of a heterocyclic lactam. No chlorination took place without DMF and no dimethylamino compounds were found among the products. Optimal conditions are given in procedure B. The crude 7-chloro compounds obtained by this method were thiated in good yields by heating with ammonium hydrosulfide solution to give the 7-thiones (IV).

Monophosphorylated derivatives of IV could be obtained in roughly quantitative yields by heating III with phosphorus pentasulfide in pyridine. Hydrolytic removal of the phosphate residues by acid or base was accompanied by hydrolysis of amino groups as indicated by the elemental analyses. Phosphorylated 7-thiones were also obtained by chlorination of the oxo compounds (III) with phosphorus pentachloride in refluxing phosphorus oxychloride and thiation of the resulting 7-chloro compounds by heating with ammonium hydrosulfide solution.

The 7-thiones (IV) were dethiated in low yields by means of activated Raney nickel catalyst to give 7-unsubstituted 2,4-diaminopyrido[2,3-*d*]pyrimidines. No other products were isolated, and the losses are attributed to absorption of the compounds on the nickel. Negligible yields, usually amounting to less than 1%, were obtained from phosphorylated 7-thiones.

The dethiated products were shown by their pmr spectra to be pyrido[2,3-*d*]pyrimidines (II). Thus, the spectrum of **38** (trifluoroacetic acid as solvent, TMS as internal standard) shown in Table I would be expected for a 2,4-diaminopyrido[2,3-*d*]pyrimidine with methyl and benzyl substituents in the pyridine ring, *i.e.*, I or II where R_1, R_2 = methyl and benzyl. However, compounds which would be obtained by the thiation and dethiation of the pyrimidopyrimidines (VIII–X) would each have two heterocyclic CH groups instead of one. The other dethiated compounds (II) prepared in this work have spectra similar to those of **38**.

TABLE I

PMR SPECTRUM OF **38** IN TRIFLUOROACETIC ACID

Chemical shift, ppm (δ)	No. of protons	Form	Assignment
3.10	3	Singlet	Aromatic CH_3
4.33	2	Singlet	Benzylic CH_2
7.30, 7.43	5	Complex	Phenyl C_6H_5
8.85	1	Singlet	Heterocyclic CH

The substitution pattern of the dethiated pyrido-[2,3-*d*]pyrimidines (II) and thus of the oxo compounds (III) is shown by comparison of two dethiated products (**46**, **48**) with known compounds. Robins and Hitchings[2] have shown that α-formyl ketones condense with 2,4,6-triaminopyrimidine to give 6,7-disubstituted 2,4-diaminopyrido[2,3-*d*]pyrimidines (Ia). They prepared 2,4-diamino-6-ethyl-7-propylpyrido[2,3-*d*]pyrimidine (Ib) and 2,4-diamino-7-phenylpyrido[2,3-*d*]-pyrimidine (Ic) by this method. The ethylpropyl derivative (**46**) and the phenyl derivative (**48**) were obtained in this work from ethyl propionylpropionate and ethyl benzoylacetate, respectively. If the condensation products of these β-keto esters with 2,4,6-triaminopyrimidine were 7,8-dihydro-7-oxopyrido[2,3-*d*]pyrimidines, then the dethiation products **46** and **48** should not be identical with Ib and Ic. If the condensation products were 5,8-dihydro-5-oxopyrido[2,3-*d*]-pyrimidines, then **46** would be identical with Ib and **48** with Ic. The uv absorption spectra of **46**, **48**, Ib, and Ic are shown in Figures 1–4. These are the spectra of four different compounds, and so **46** is shown to be 2,4-diamino-6-ethyl-5-propylpyrido[2,3-*d*]pyrimidine, and **48** is 2,4-diamino-5-phenylpyrido[2,3-*d*]pyrimidine. The uv spectra of the 5,6-disubstituted derivatives (II) differ from the spectra of the 6,7-disubstituted isomers (I) in having lower intensities for the long-wavelength absorption band (*cf.* **46** and Ib). The long-wavelength absorption band of the 5-phenyl derivative (**48**) appears at a lower intensity and shorter wavelength than the equivalent bands of the 6-phenyl[8]

(7) J. Žemlička, J. Smrt, and F. Šorm, *Tetrahedron Letters*, 397 (1962).

(8) B. S. Hurlbert and B. F. Valenti, *J. Med. Chem.*, **11**, 708 (1968), paper XXIV in this series.

TABLE II
ULTRAVIOLET SPECTRA AND pK_a VALUES OF REPRESENTATIVE 2,4-DIAMINOPYRIDO[2,3-*d*]PYRIMIDINES

Compd	λ_{max}, mμ (ε × 10^{-3}) pH 2	pH 11	pK_a
4	295[a]	325	
	321		
10	320	235	
		332	
13	222 (10.9)	231 (5.1)	
	296 (3.7)	286 (1.8)	
	318 (4.1)	325 (3.1)	
17	223 (26.1)	250[a] (9.2)	
	297[a] (12.8)	284 (5.6)	
	322 (16.6)	328 (15.6)	
22	210 (16.2)	250[a] (5.9)	
	297[a] (6.9)	330 (7.5)	
	322 (8.2)		
25	232 (34.3)	239 (34.3)	
	322 (9.3)	364 (10.8)	
	332[a] (8.8)		
	391 (9.6)		
27	230 (30.0)	239 (25.4)	
	325[a] (10.5)	270[a] (9.4)	
	333 (11.1)	355 (7.5)	
	350[a] (8.4)		
	363[a] (7.2)		
31	267 (9.3)	265[a] (6.5)	7.1
	321 (7.2)	345 (6.1)	
	330[a] (6.6)		
38	232 (34.1)	235 (30.6)	7.0
	320 (7.6)	343 (6.4)	
46	232 (32.7)	236 (31.1)	7.1
	322 (7.7)	343 (6.5)	
48	274 (10.1)	249 (26.0)	6.7
	316 (8.5)	267[a] (12.2)	
	325[a] (8.0)	346 (6.4)	
49	275 (7.4)	248 (25.3)	
	322 (11.1)	342 (8.9)	
	330[a] (10.1)		
Ib	225 (34.4)	267 (9.1)	7.1
	321 (11.7)	346 (8.9)	
	333 (10.7)		
	373 (1.5)		
Ic	222 (31.5)	236 (24.7)	6.8
	248 (15.2)	259 (28.2)	
	337 (23.6)	356 (13.1)	

[a] Inflection.

and 7-phenyl (Ic) derivatives. These effects may be due to an inhibition of resonance caused by steric repulsion between the 4-amino group and the 5 substituent.

Some representative spectra and thermodynamic pK_a values for 2,4-diaminopyrido[2,3-*d*]pyrimidines are given in Table II. The pK_a values were determined spectrometrically using dilute phosphate buffers according to the published method.[9] The 2,4-diaminopyrido[2,3-*d*]pyrimidines I and II were found to have pK_a values close to 7 which is reasonable when compared with the basicities of other 2,4-diaminopyrimidine systems prepared in this laboratory.[10] Compounds derived from VII–X would be expected to be much stronger bases.

The biological properties of the compounds are discussed in a following paper.[11]

(9) A. Albert and E. P. Serjeant, "Ionization Constants of Acids and Bases," John Wiley and Sons, Inc., New York, N. Y., 1962.
(10) B. Roth and J. Strelitz, private communication.
(11) B. S. Hurlbert, R. Ferone, T. A. Herrmann, G. H. Hitchings, M. Barnett, and S. R. M. Bushby, *J. Med. Chem.*, **11**, 711 (1968).

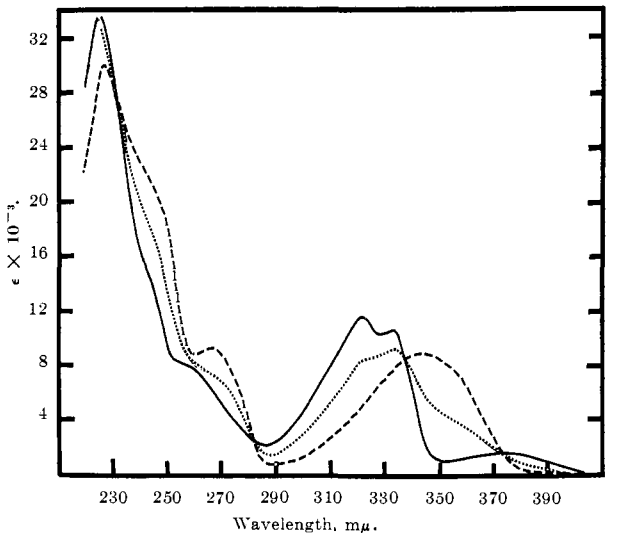


Figure 1.—Ultraviolet spectrum of 2,4-diamino-6-ethyl-7-propylpyrido[2,3-*d*]pyrimidine (Ib, pK_a = 7.26): ——, spectrum of protonated form; - - - - - - -, spectrum of neutral molecule; · · · · ·, spectrum at pK_a.

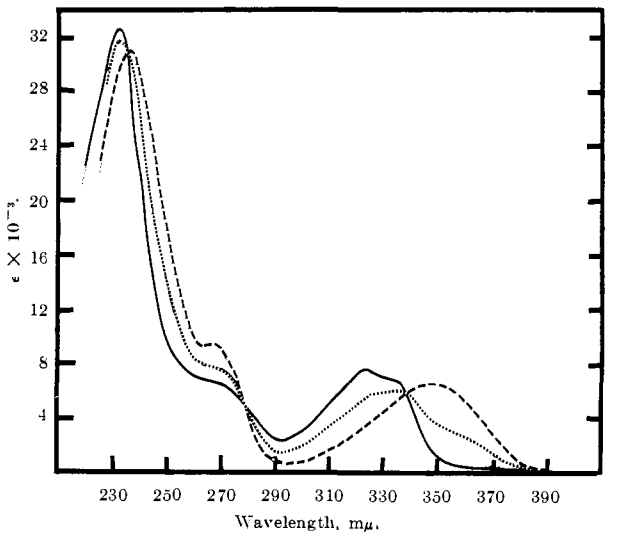


Figure 2.—Ultraviolet spectrum of 2,4-diamino-6-ethyl-5-propylpyrido[2,3-*d*]pyrimidine (**46**, pK_a = 7.28): ——, spectrum of protonated form; - - - - - - -, spectrum of neutral molecule; · · · · ·, spectrum at pK_a.

Experimental Section

Uv spectra were determined on Beckman DU and Cary 15 spectrophotometers, nmr data on a Varian A-60 instrument.

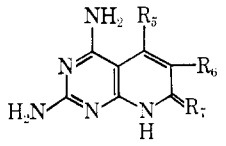
All 7-oxo compounds reported in Table III were prepared by the following method.

6-Benzyl-2,4-diamino-7,8-dihydro-5-methyl-7-oxopyrido[2,3-*d*]pyrimidine.—A mixture of ethyl α-benzylacetoacetate (100 g, 0.455 mole) and 2,4,6-triaminopyrimidine (57 g, 0.455 mole) in 450 ml of Ph_2O was heated with stirring at 190–225° until distillation of low-boiling materials (EtOH, H_2O) ceased. The mixture was cooled and, an equal volume of MeOH was added. This mixture was filtered and the solid was washed with MeOH. The solid was then suspended in 1.5 l. of boiling H_2O, filtered while hot, and washed again with MeOH to yield 77.8 g (61%).

Three methods of preparation of the 7-thiones were used and are illustrated by the preparation of the 6-benzyl-5-methyl derivative by each method. Method B gave the best yields of pure products with all derivatives.

6-Benzyl-2,4-diamino-7,8-dihydro-5-methylpyrido[2,3-*d*]pyrimidine-7-thione. A.—A mixture of 6-benzyl-2,4-diamino-7,8-dihydro-5-methyl-7-oxopyrido[2,3-*d*]pyrimidine (77.2 g, 0.274 mole) and PCl_5 (77.0 g, 0.37 mole) in 800 ml of $POCl_3$ was heated

TABLE III



No.	R_5	R_6	R_7	Yield, %	Mp, °C[a]	Formula	Analyses
1	CH_3	H	O	57	>360	$C_8H_9N_5O \cdot C_2H_4O_2$[b]	C, H, N
2	CH_3	CH_3	O	24		$C_9H_{11}N_5O$	C, H, N
3	CH_3	C_3H_7	O	23		$C_{11}H_{15}N_5O$	C, H; N[c]
4	CH_3	C_4H_9	O	50		$C_{12}H_{17}N_5O$	C, H, N
5	CH_3	$CH(CH_3)C_2H_5$	O	35		$C_{12}H_{17}N_5O$	H, N; C[d]
6	CH_3	C_5H_{11}	O	65	335 dec	$C_{13}H_{19}N_5O$	C, H, N
7	CH_3	$CH_2CH_2CH(CH_3)_2$	O	51	>340 dec	$C_{13}H_{19}N_5O$	C, H, N
8	CH_3	$CH(CH_3)C_3H_7$	O	30		$C_{13}H_{19}N_5O$	H, N; C[e]
9	CH_3	C_6H_{13}	O	54		$C_{14}H_{21}N_5O$	C, H; N[f]
10	CH_3	C_7H_{15}	O	21		$C_{15}H_{23}N_5O$	C, H, N
11	CH_3	$CH_2C_6H_5$	O	61		$C_{15}H_{15}N_5O$	C, H, N
12	CH_3	p-$CH_2C_6H_4CH_3$	O	56		$C_{16}H_{17}N_5O$	C, H, N
13	CH_3	p-$CH_2C_6H_4Cl$	O	43	392–394	$C_{15}H_{14}N_5OCl$	C, H, N
14	CH_3	p-$CH_2C_6H_4OCH_3$	O	51		$C_{16}H_{17}N_5O_2$	C, H, N
15	CH_3	o-$CH_2C_6H_4Cl$	O	51		$C_{15}H_{14}N_5OCl$	H; C, N[g]
16	CH_3	o-$CH_2C_6H_4OCH_3$	O	49	>300	$C_{16}H_{17}N_5O_2$	C, H, N
17	C_2H_5	$CH_2C_6H_5$	O	51	>320	$C_{16}H_{17}N_5O$	C, H, N
18	C_3H_7	H	O			$C_{10}H_{13}N_5O$	C, H, N
19	C_3H_7	C_2H_5	O	60	350 dec	$C_{12}H_{17}N_5O$	C, H, N
20	C_3H_7	$CH_2C_6H_5$	O	31		$C_{17}H_{19}N_5O$	C, H, N
21	C_6H_5	H	O	42		$C_{13}H_{11}N_5O$	C, H; N[h]
22	C_6H_5	$CH_2C_6H_5$	O	19	>300	$C_{20}H_{17}N_5O \cdot H_2O$	H, N; C[i]
23	$-(CH_2)_4-$		O	26	>350	$C_{11}H_{13}N_5O$	C, H, N
24	CH_3	$CH(CH_3)C_2H_5$	S			$C_{12}H_{17}N_5S$	C, H, N
25	CH_3	$CH_2C_6H_5$	S	52[j]		$C_{15}H_{15}N_5S \cdot 0.5H_2O$	C, H; N[k]

[a] Where no melting point is given, compound decomposed without melting. [b] Acetate salt. [c] N: calcd, 30.02; found, 30.62. [d] C: calcd, 58.28; found, 58.82. [e] C: calcd, 59.75; found, 59.11. [f] N: calcd, 25.44; found, 24.71. [g] C: calcd, 57.05; found 57.71. N: calcd, 22.18; found, 21.01. [h] N: calcd, 27.66; found, 27.02. [i] C: calcd, 69.95; found 69.09. [j] Yield from **27**. [k] N: calcd, 22.86; found, 21.88.

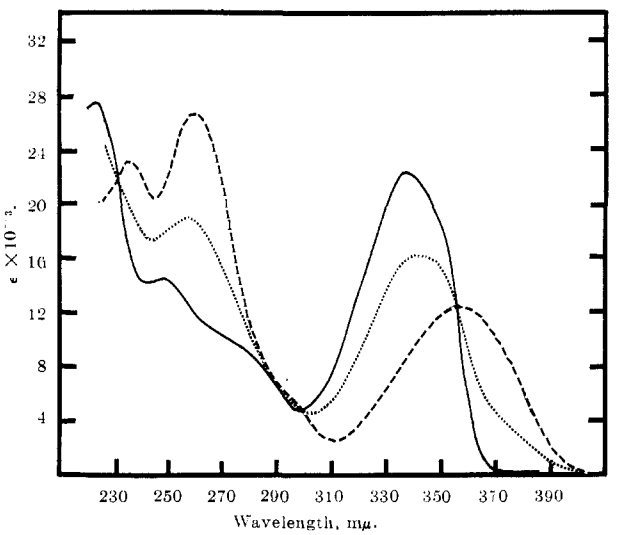


Figure 3.—Ultraviolet spectrum of 2,4-diamino-7-phenylpyrido[2,3-*d*]pyrimidine (Ic, pK_a = 6.93): ——, spectrum of protonated form; - - - - - - - -, spectrum of neutral molecule; · · · · ·, spectrum at pK_a.

at reflux for 6 hr. The $POCl_3$ was then distilled *in vacuo* to leave a viscous residue which was poured onto ice and neutralized with concentrated NaOH while stirring vigorously and keeping the temperature below 10°. Stirring was continued for 1 hr, and the mixture was allowed to stand at 10° for 18 hr. It was then filtered, and the solids were washed thoroughly with H_2O. The solid product was a phosphorylated 6-benzyl-7-chloro-2,4-diamino-5-methylpyrido[2,3-*d*]pyrimidine and was thiated without further purification.

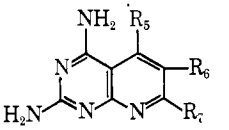
A solution of NH_4SH was prepared by saturating 1200 ml of 5 *M* NH_4OH with H_2S. The phosphorylated 6-benzyl-7-chloro-2,4-diamino-5-methylpyrido[2,3-*d*]pyrimidine was heated in this solution in a steel bomb for 1 hr at 100°. After cooling, the reaction mixture was filtered, and the precipitate was washed with H_2O to yield 62 g of phosphorylated 6-benzyl-2,4-diamino-7,8-dihydro-5-methylpyrido[2,3-*d*]pyrimidine-7-thione.

B.—A mixture of 6-benzyl-2,4-diamino-7,8-dihydro-5-methyl-7-oxopyrido[2,3-*d*]pyrimidine (2.81 g, 0.01 mole), DMF (7.3 g, 0.1 mole), $SOCl_2$ (11.9 g, 0.1 mole), and 25 ml of $CHCl_3$ was heated under reflux for 1.5 hr, and concentrated *in vacuo* at 50° to leave a viscous residue. The residue was dissolved in 150 ml of 50% EtOH–H_2O and made basic to a pH of 10 by addition of 2 *N* NaOH. A precipitate formed which was filtered, washed with H_2O, and recrystallized from 30% H_2O–EtOH to yield 1.30 g of 6-benzyl-7-chloro-2,4-diamino-5-methylpyrido[2,3-*d*]pyrimidine.

This 7-chloro compound (2 g, 0.007 mole) was heated with 200 ml of NH_4SH solution in a steel bomb at 120° for 2 hr. After cooling, the reaction mixture was filtered; the precipitate was washed with H_2O and recrystallized from 30% H_2O–EtOH to yield 1.05 g of 6-benzyl-2,4-diamino-7,8-dihydro-5-methylpyrido-[2,3-*d*]pyrimidine-7-thione.

C.—6-Benzyl-2,4-diamino-7,8-dihydro-5-methyl-7-oxopyrido-[2,3-*d*]pyrimidine (307 g, 1.09 moles) and P_2S_5 (300 g, 1.35 moles) in 2400 ml of pyridine were heated at reflux for 1 hr and concentrated *in vacuo* to leave a solid residue. This residue was stirred with 3 l. of boiling H_2O, and the mixture was acidified to a pH of 5 with HCl. It was filtered while hot, and the precipitate was washed with hot H_2O. It was stirred again with hot H_2O, filtered, and dried; 432 g of product was obtained. A sample of this product, after heating with HNO_3, was found to contain ionic phosphate. Brief treatment with dilute acid or NH_3 did not remove any phosphate; prolonged heating in dilute acid eventually removed the phosphate but gave a product with an N content lower than that of the expected material, indicating the loss of amino groups as well as phosphate. It is therefore as-

TABLE IV



No.	R_5	R_6	R_7	Yield,[a] %	Mp, °C[b]	Formula	Analyses
26	CH_3	$CH(CH_3)C_2H_5$	Cl		242	$C_{12}H_{16}N_5Cl$	C, H, N
27	CH_3	$CH_2C_6H_5$	Cl	43	326	$C_{15}H_{14}N_5Cl$	C, N; H[c]
28	CH_3	H	H		320 dec	$C_8H_9N_5$	C, H, N
29	CH_3	CH_3	H		310 dec	$C_9H_{11}N_5$	H, N; C[d]
30	CH_3	C_3H_7	H		290 dec	$C_{11}H_{15}N_5$	C, H, N
31	CH_3	C_4H_9	H			$C_{12}H_{17}N_5$	C, H, N
32	CH_3	$CH(CH_3)C_2H_5$	H		248–249	$C_{12}H_{17}N_5 \cdot 0.5H_2O$	C, H, N
33	CH_3	C_5H_{11}	H		251–254	$C_{13}H_{19}N_5 \cdot HCl$	C, H, N
34	CH_3	$CH_2CH_2CH(CH_3)_2$	H		291 dec	$C_{13}H_{19}N_5$	C, H, N
35	CH_3	$CH(CH_3)C_3H_7$	H		216–218	$C_{13}H_{19}N_5$	C, H, N
36	CH_3	C_6H_{13}	H		264 dec	$C_{14}H_{21}N_5$	C, H, N
37	CH_3	C_7H_{15}	H		282 dec	$C_{15}H_{23}N_5$	C, H, N
38	CH_3	$CH_2C_6H_5$	H	22	308 dec	$C_{15}H_{15}N_5 \cdot 0.5H_2O$	C, H, N
39	CH_3	p-$CH_2C_6H_4CH_3$	H	18		$C_{16}H_{17}N_5 \cdot H_2O$	C, H; N[e]
40	CH_3	p-$CH_2C_6H_4Cl$	H	12	275–277	$C_{15}H_{14}N_5Cl \cdot 0.5H_2O$	C, H; N[f]
41	CH_3	p-$CH_2C_6H_4OCH_3$	H	11		$C_{16}H_{17}N_5O \cdot HCl$	C, H, N
42	CH_3	o-$CH_2C_6H_4Cl$	H	7	208	$C_{15}H_{14}N_5Cl \cdot C_2H_6O_3S$[g]	C, H, N
43	CH_3	o-$CH_2C_6H_4OCH_3$	H	17		$C_{16}H_{17}N_5O \cdot HCl \cdot H_2O$	C, H, N
44	C_2H_5	$CH_2C_6H_5$	H			$C_{16}H_{17}N_5 \cdot HCl \cdot H_2O$	C, H, N
45	C_3H_7	H	H		292 dec	$C_{10}H_{13}N_5$	C, H, N
46	C_3H_7	C_2H_5	H		200 dec	$C_{12}H_{17}N_5 \cdot HCl \cdot H_2O$	C, H, N
47	C_3H_7	$CH_2C_6H_5$	H		>300 dec	$C_{17}H_{19}N_5 \cdot 0.5H_2O$	C, H; N[h]
48	C_6H_5	H	H		360 dec	$C_{13}H_{11}N_5$	N; C, H[i]
49	C_6H_5	$CH_2C_6H_5$	H	27	>320	$C_{20}H_{17}N_5 \cdot 0.5H_2O$	C, H, N
50		$-(CH_2)_4-$	H		337 dec	$C_{11}H_{13}N_5$	C, H, N

[a] Yields are for conversion of 7-oxo compounds to the products described by treatment with $SOCl_2$ in DMF and $CHCl_3$ followed, where appropriate, by NH_4SH and Raney Ni dethiation. [b] Where no melting point is given, compound decomposed without melting. [c] H: calcd, 4.71; found, 5.38. [d] C: calcd, 57.13; found 56.68. [e] N: calcd, 20.98; found, 20.04. [f] N: calcd, 22.68; found, 21.41. [g] Isethionate salt. [h] N: calcd, 23.17; found, 22.66. [i] C: calcd, 65.80; found, 65.39. H: calcd, 4.67; found, 4.07.

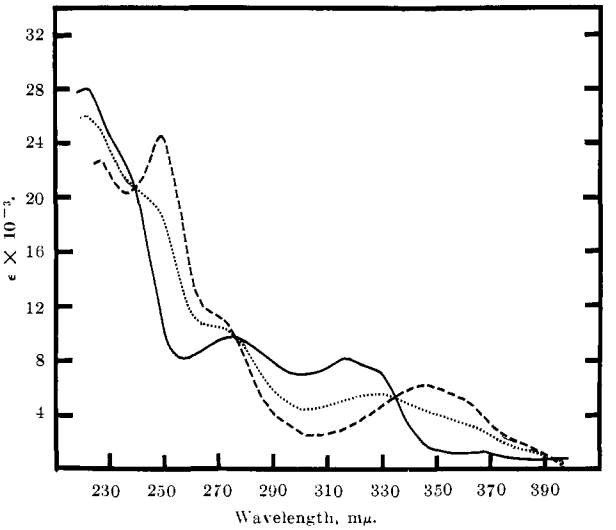


Figure 4.—Ultraviolet spectrum of 2,4-diamino-5-phenylpyrido[2,3-*d*]pyrimidine (**48**, pK_a = 6.73): ——, spectrum of protonated form; - - - - - - - -, spectrum of neutral molecule; · · · · ·, spectrum at pK_a.

sumed that the crude product was a phosphorylated 6-benzyl-2,4-diamino-7,8-dihydro-5-methylpyrido[2,3-*d*]pyrimidine-7-thione.

All dethiations were carried out by the following method. The compounds are shown in Table IV.

6-Benzyl-2,4-diamino-5-methylpyrido[2,3-*d*]pyrimidine.—The phosphorylated 6-benzyl-2,4-diamino-7,8-dihydro-5-methylpyrido[2,3-*d*]pyrimidine-7-thione (20 g) prepared by method C was suspended in a solution of 100 ml of 15 *M* NH_4OH and 1 l. of EtOH and boiled under reflux with vigorous stirring; no. 28 active Raney Ni (Raney Catalyst Co.) in H_2O was added in batches at 0.5-hr intervals until the uv absorption of the 7-thione at 395 mμ in acid solution had disappeared. The mixture was filtered hot and the Ni was washed with hot EtOH. The combined filtrates were treated with charcoal while hot, filtered, and evaporated to a small volume. The material which crystallized from this solution was recrystallized from 30% H_2O–EtOH to yield 4.5 g of product.

Bisdichlorophosphoryl-7-chloro-2,4-diamino-5-ethyl-6-methylpyrido[2,3-*d*]pyrimidine.—2,4-Diamino-7,8-dihydro-5-ethyl-6-methyl-7-oxopyrido[2,3-*d*]pyrimidine (219 g, 1.0 mole) and PCl_5 (239 g, 1.15 moles) were heated in 1800 ml of $POCl_3$ at reflux for 5 hr. The $POCl_3$ was then distilled *in vacuo*. The oily residue was poured slowly, with stirring, into cold hexane. The solid which separated was filtered and washed with hexane. After drying *in vacuo* over solid NaOH, 492 g of product was obtained. This represents 104% yield of 7-chloro-2,4-diamino-5-ethyl-6-methylpyrido[2,3-*d*]pyrimidine with two dichlorophosphoryl groups.

Anal. Calcd for $C_{10}H_{10}N_5Cl \cdot (POCl_2)_2$: C, 25.47; H, 2.14; N, 14.86; P, 13.14. Found: C, 25.05; H, 2.28; N, 15.56; P, 15.38.

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