JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

(Registered in U. S. Patent Office)

VOLUME 71 JULY 21, 1949 NUMBER 7

[CONTRIBUTION FROM THE WELLCOME RESEARCH LABORATORIES]

A Synthesis of 4-Amino-2-thiolpyrimidines

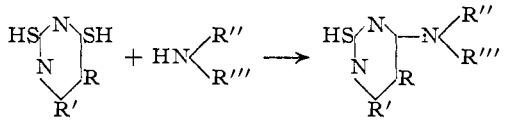
BY PETER B. RUSSELL, GERTRUDE B. ELION, ELVIRA A. FALCO AND GEORGE H. HITCHINGS

The reaction of 2,4-dithiolpyrimidine derivatives with ammonia and amines leads, as will be shown, exclusively to 4-amino-2-thiolpyrimidines. The unidirectional course of this reaction may be contrasted with the similar reactions of 2,4-dichloro-[1] and 2,4-diethoxypyrimidines[2] which lead invariably to mixtures of isomers. Since 2,4-dithiolpyrimidines are readily available from uracils, thiouracils and 2-ethylmercapto-4-hydroxypyrimidines[3] the reaction of the dithiol derivatives with amines provides a convenient route to the synthesis of 4-amino-2-thiolpyrimidines and a number of aminohydroxy, amino and diaminopyrimidines which hitherto have been accessible only by roundabout methods.

The conversion of thioamides to amidines by treatment with ammonia is a well-known reaction,[4] but only a few applications of the reaction to heterocyclic compounds have appeared in the literature. Carrington[5,6] converted 2,4-dithiobarbituric acids to the corresponding 4-imino-2-thio derivatives, and 2,4-dithiohydantoins to 4-imino-2-thiohydantoins by treatment with ammonia. The reaction of 4-thiolquinazolines with amines also has been reported.[7,8]

The reaction of 2,4-dithiolpyrimidines with amines has been found to be quite general, being limited only by certain steric considerations which will be discussed. The first product appears invariably to be the 4-amino-2-thiolpyrimidine[9] which usually is obtained in excellent yield. These products, in a number of instances, were identified by conversion to known substances. Thus, 4-amino-2-thiolpyrimidine was identified by its conversion to cytosine and 4-amino-5-methyl-2-thiolpyrimidines to 5-methylcytosine.[10] The treatment of 2,4-dithiolquinazoline with ammonium hydroxide gave a thiolamino derivative which was hydrolyzed to the known 4-hydroxy-2-thiolquinazoline. The 4-anilino-2-thiolpyrimidine, obtained by the reaction of dithiouracil with aniline, was identified by conversion to N-phenylcytosine, 4-anilino-2-ethylmercaptopyrimidine and to 4-anilinopyrimidine, all known compounds.

The limitations of the reaction between dithiolpyrimidines and amines appear to be determined by steric factors. When the dithiolpyrimidine is



I II III

unsubstituted in the 5-position (I, R = H) the pyrimidine reacts readily with ammonia, primary aliphatic and aromatic amines (II, R″ = H, R‴ = alkyl or aryl), cyclic secondary amines (II, R″ and R‴ = $-CH_2CH_2-X-CH_2CH_2-$ where X may be CH_2, O or NCH_3) and secondary aliphatic and aromatic amines in which at least one of the substituents is a methyl group (II, R″ = Me, R‴ = alkyl or aryl). The reaction fails with diethylamine and higher secondary

(1) Hilbert and Johnson, THIS JOURNAL, **52**, 1152 (1930).

(2) Hilbert, Jansen and Hendricks, *ibid.*, **57**, 552 (1935).

(3) Elion and Hitchings, *ibid.*, **69**, 2138 (1947).

(4) Sidgwick, "Organic Chemistry of Nitrogen," 2nd ed., Oxford University Press, London, 1937, p. 151.

(5) Carrington, *J. Chem. Soc.*, 124 (1944).

(6) Carrington, *ibid.*, 684 (1947).

(7) Leonard and Curtin, *J. Org. Chem.*, **11**, 349 (1946).

(8) Tomisek and Christensen, THIS JOURNAL, **70**, 2423 (1948).

(9) In a single instance a diamino derivative was isolated. When 2,4-dithiol-6-methylpyrimidine was heated for sixty-eight hours at 120° with a large excess of ammonium hydroxide, 2,4-diamino-6-methylpyrimidine was obtained in 25% yield. At 100° for eighteen hours a 60% yield of 4-amino-6-methyl-2-thiolpyrimidine was obtained. In neither experiment could a second product be isolated.

(10) Hitchings, Elion, Falco and Russell, *J. Biol. Chem.*, **177**, 357 (1949).

amines.[11] The size and nature of the alkyl group of the primary amines appear to be of little importance for the reaction takes place as readily with tetradecylamine, β-hydroxyethylamine and β-morpholinoethylamine as with methylamine. Aromatic amines also react readily, although a somewhat higher reaction temperature usually is required. Substituents in the 6-position of the pyrimidine ring (I, R = H, R′ = alkyl or aryl) appear to have little influence on the course of the reaction, 6-methyl-2,4-dithiol- and 6-phenyl-2,4-dithiolpyrimidine giving essentially the same reactions as dithiouracil.

When the pyrimidine ring is substituted in the 5-position (I, R = alkyl, aryl or aryloxy) some limitations of the reaction are at once apparent. The reaction proceeds as above with primary aliphatic and aromatic amines. However, secondary amines of all types fail to react as evidenced by the recovery of the starting material and absence of evolution of hydrogen sulfide. Certain heavily hindered amines such as benzohydrylamine also fail to yield the desired aminopyrimidine.[12] The results leave little doubt that the reaction may be blocked decisively by steric hindrance. Incidentally, these experiments serve also to emphasize the difference in reactivity between the 2- and 4-thiol groups. Blocking in the 4-position would be expected to favor any tendency to reaction in the 2-position, but even under such conditions no 2-amino derivatives were formed.

Experimental

Dithiolpyrimidines.—The preparations of dithiouracil, dithiothymine and dithiolquinazoline have been described earlier.[3] 6-Methyl-dithiouracil[13] was prepared by the same procedure from 6-methyl-2-thiouracil at 190–200° for three hours.

5-Benzyl-2,4-dithiolpyrimidine.—A mixture of 2.4 g. of 5-benzyluracil[14] and 6.5 g. of phosphorus pentasulfide in 40 ml. of tetralin was heated with stirring at 200° for two and one-half hours. After cooling, the solid was filtered off, washed with petroleum ether and dissolved in 200 ml. of water by the addition of 10 ml. of 2.5 *N* sodium hydroxide solution. The alkaline solution was treated with charcoal, filtered and the filtrate acidified with hydrochloric acid. On recrystallization from ethanol the yellow precipitate (2.5 g.) formed long yellow needles, m. p. 262° (dec.).

Anal. Calcd. for $C_{11}H_{10}N_2S_2$: C, 56.4; H, 4.3. Found: C, 56.3; H, 4.3.

5-Phenoxy-2,4-dithiolpyrimidine.—A mixture of 15 g. of 4-hydroxy-5-phenoxy-2-thiolpyrimidine[15] and 40 g. of phosphorus pentasulfide in 150 ml. of tetralin was heated with stirring at 200° for two hours. After cooling, the solid was filtered off, washed with petroleum ether, dissolved in 500 ml. of water by the addition of an excess of potassium hydroxide solution and precipitated by acidification with acetic acid. After a second purification by the same procedure the yield was 8 g. The yellow crystalline powder obtained by recrystallization from ethanol melted at 287° (dec.).

Anal. Calcd. for $C_{10}H_8N_2OS_2$: C, 50.9; H, 3.4. Found: C, 51.1; H, 3.2.

6-Amino-2,4-dithiolquinazoline.—A mixture of 5 g. of *p*-nitrobenzoyleneurea[16] and 15 g. of phosphorus pentasulfide in 75 ml. of tetralin and heated at 160–180° for two hours, with mechanical stirring. After cooling, the dark yellow solid was filtered off, washed with petroleum ether and dissolved in 600 ml. of hot water by the addition of 50 ml. of 2.5 *N* sodium hydroxide solution. The hot solution was filtered and immediately acidified with acetic acid. The orange-colored amorphous precipitate was redissolved in 300 ml. of 0.25 *N* sodium hydroxide solution at room temperature, treated with charcoal and reprecipitated with acetic acid (3.8 g., 75%). The compound is nearly insoluble in water and organic solvents and does not melt below 390°. Analysis indicated that reduction of the nitro group had occurred although the aminodithiolquinazoline was not completely pure. This was confirmed by its transformation to 4,6-diamino-2-thiolquinazoline (Table I).

Anal. Calcd. for $C_8H_7N_3S_2$: C, 45.9; H, 3.4. Found: C, 45.1; H, 3.2.

4-Amino-2-thiolpyrimidines. General Method.—The dithiolpyrimidine and 3 molar equivalents of amine are mixed, whereupon the pyrimidine usually dissolves with liberation of heat. The solution is heated at the temperature and under the conditions indicated in Table I for three hours in an open system, or overnight (sixteen hours) in a sealed tube. The course of the reaction, in the open system, can be followed by the evolution of hydrogen sulfide. The product separates during the course of the reaction in most instances. The residual amine is removed by evaporation or diluted with a suitable solvent (ether, water or ethanol) and the product is filtered off and washed with the same solvent. The product is recrystallized from water, aqueous or absolute ethanol. Two examples of these procedures are given below in addition to the data of Table I.

4-Methylamino-2-thiolpyrimidine.—Dithiouracil (1.3 g.) was heated with 10 ml. of 33% aqueous methylamine solution in a sealed tube at 100° for three and one-half hours. The solution was evaporated to dryness and the product was recrystallized from hot water, giving short colorless prisms, m. p. 236–237°; yield 0.85 g. (60%).

4-Anilino-6-methyl-2-thiolpyrimidine.—A mixture of 6-methyldithiouracil (0.65 g.) and aniline (2 ml.) was refluxed for three hours. The excess aniline was removed with ether. The product was washed with concentrated ammonium hydroxide to dissolve any unchanged dithiol derivative, and was recrystallized from hot water; yield 0.92 g. (80%).

4-Hydroxy-2-thiolquinazoline.—Ninety milligrams of 4-amino-2-thiolquinazoline was heated with 10 ml. of 2.5 *N* hydrochloric acid on the steam-bath for four hours. After a short time the solid dissolved and a colorless crystalline precipitate formed gradually during the course of the heating. This precipitate, m. p. 290–293° (dec.), (80 mg., 90%) was identified as 2-thiol-4-hydroxyquinazoline by its ultraviolet absorption spectrum which is identical with that of an authentic specimen prepared from anthranilic acid by the action of potassium thiocyanate. In 0.1 *N* hydrochloric acid: $\lambda_{max.}$ = 2850 Å., E_m = 23,000; in a glycine-sodium hydroxide buffer of *p*H 11, $\lambda_{max.}$ = 2820 Å., E_m = 17,500.

(11) The failure of the higher secondary aliphatic amines to react was strikingly illustrated by an experiment in which di-*n*-amylamine containing a few per cent. of *n*-amylamine was heated with dithiouracil. The only product isolated was 4-*n*-amylamino-2-thiolpyrimidine.

(12) Benzohydrylamine and dithiothymine gave no evidence of reaction at 110–120°, but when the temperature was raised to 175°, hydrogen sulfide was evolved smoothly over a period of two and one-half hours. However, the only substance which could be isolated from the reaction mixture in addition to unchanged dithiothymine was dibenzohydrylamine. Since benzohydrylamine is stable at this temperature, it appears that the normal pyrimidine derivative may have been formed first, followed by cleavage and reaction of the benzohydryl ion with a second molecule of the amine (*cf.* Cantarel, *Compt. rend.*, **226**, 931 (1948); **227**, 286 (1948)).

(13) Gabriel and Colman, *Ber.*, **32**, 2921 (1899).

(14) Johnson and Ambelang, THIS JOURNAL, **60**, 2941 (1938).

(15) Johnson and Guest, *Am. Chem. J.*, **42**, 271 (1909).

(16) Bogert and Scatchard, THIS JOURNAL, **41**, 2052 (1919).

TABLE I

PRODUCTS OF REACTION OF DITHIOLPYRIMIDINES HS(N—SH)(N—R′)R WITH VARIOUS AMINES,

R	R′	Amine	Conditions[a]	Yield, %	M. p., °C.	Empirical formula	Analyses, % Calcd. C	Calcd. H	Found C	Found H
H	H	NH_3	S. T.[b] 29% aq. soln.	91	278 (dec.)	$C_4H_5N_3S$	37.8	3.9	38.2	4.2
H	H	CH_3NH_2	3.5 Hr. S. T. 25% aq. soln.	60	236–237	$C_5H_7N_3S$	42.6	5.0	42.5	5.0
H	H	n-$C_5H_{11}NH_2$		85	218	$C_9H_{15}N_3S$	54.9	7.6	55.2	7.5
H	H	n-$C_{14}H_{29}NH_2$		80	148–149	$C_{18}H_{33}N_3S$	66.9	10.0	66.6	9.9
H	H	$PhCH_2NH_2$		75	248–249	$C_{11}H_{11}N_3S$	60.9	5.1	60.6	5.0
H	H	Ph_2CHNH_2	110°	70	250–260 (dec.)	$C_{17}H_{15}N_3S$	69.6	5.1	69.4	4.9
H	H	$HOCH_2CH_2NH_2$		82	226–228	$C_6H_9N_3OS$	42.2	5.3	42.6	5.2
H	H	$(C_2H_5)_2NCH_2CH_2NH_2$		50	114–115	$C_{10}H_{18}N_4S$	53.1	8.0	52.8	8.1
H	H	β-Morpholino-ethyl-amine	110°	85	242–243 (dec.)	$C_{10}H_{16}N_4OS$	50.0	6.8	50.3	6.6
H	H	Morpholine		65	248–250	$C_8H_{11}N_3OS$	48.7	5.5	48.8	5.5
H	H	Piperidine		60	227–228	$C_9H_{13}N_3S$	55.4	6.7	55.6	6.6
H	H	N-Methylpiperazine		60	257	$C_9H_{14}N_4S$	51.5	6.7	51.5	6.4
H	H	$(CH_3)_2NH$	3.5 Hr. S. T. 130° 33% EtOH soln.	55	280–283 (dec.)	$C_6H_9N_3S$	46.5	5.8	46.4	5.5
H	H	n-$C_3H_7NHCH_3$	10 Hr. S. T.	50	194–195	$C_8H_{13}N_3S$	52.5	7.1	52.4	6.8
H	H	$(C_2H_5)_2NH$	S. T. 140°	0						
H	H	$(n$-$C_5H_{11})_2NH$[11]	150°	0						
H	H	Ph_2NH	180°	0						
H	H	Aniline	Reflux	90	285 (dec.)	$C_{10}H_9N_3S$	59.1	4.5	59.1	4.6
H	H	p-Chloroaniline	180	90	299 (dec.)	$C_{10}H_8ClN_3S$	50.5	3.4	50.2	3.2
H	H	p-CH_3O-aniline	180	85	264.5	$C_{11}H_{11}N_3OS$	56.7	4.7	57.0	4.9
H	H	N-Methylaniline	185	40	250–253	$C_{11}H_{11}N_3S$	60.9	5.1	60.5	4.7
H	CH_3	NH_3	S. T. 29% aq. soln.	60		[12,13]				
H	CH_3	n-$C_5H_{11}NH_2$		75	221 (dec.)	$C_{10}H_{17}N_3S$	56.8	8.1	56.8	7.8
H	CH_3	Piperidine	Reflux	85	203–205	$C_{10}H_{15}N_3S$	57.5	7.2	57.9	7.1
H	CH_3	Aniline	Reflux	80	230 (dec.)	$C_{11}H_{11}N_3S$	60.9	5.1	60.6	5.2
H	Ph	n-$C_5H_{11}NH_2$		68	227–228	$C_{15}H_{19}N_3S$	66.0	6.9	65.8	6.6
CH_3	H	NH_3	S. T. 29% aq. soln.	95	273–274 (dec.)	$C_5H_7N_3S$	42.6	5.0	42.3	4.9
CH_3	H	n-$C_5H_{11}NH_2$		60	198	$C_{10}H_{17}N_3S$	56.8	8.1	57.1	8.1
CH_3	H	$(CH_3)_2NH$	S. T. 120° 33% EtOH soln.	0		80% starting material recovered				
CH_3	H	Piperidine	Reflux	0		80% starting material recovered				
CH_3	H	Morpholine	5 hours	0		73% starting material recovered				
CH_3	H	Aniline	Reflux	68	232–234	$C_{11}H_{11}N_3S$	60.9	5.1	60.6	5.2
$PhCH_2$	H	CH_3NH_2	10 hr. S. T. 25% aq. soln.	58	247–248 (dec.)	$C_{12}H_{13}N_3S$	62.4	5.6	62.6	5.6
PhO	H	NH_3	26 hr. S. T. 29% aq. soln.	43	270 (dec.)	$C_{10}H_9N_3OS$	55.0	4.1	55.1	4.0
—CH=CH—CH=CH—		NH_3	29% aq. soln.	80	290–293 (dec.)	$C_8H_7N_3S$	N, 23.7		23.6	
—CH=C(NH_2)—CH=CH—		NH_3	29% aq. soln.	66	.....	$C_8H_8N_4S$	50.0	4.2	49.6	4.3

[a] The mixtures are heated at 100° in an open system with no solvent for three hours unless otherwise specified. [b] S. T. = sealed tube heated for sixteen hours unless otherwise specified.

6-Amino-4-hydroxy-2-thiolquinazoline.—A solution of 2.67 g. of 4,6-diamino-2-thiolquinazoline in 100 ml. of 2 *N* hydrochloric acid was refluxed for three hours. The brown crystalline precipitate which formed was purified by solution in 250 ml. of water containing 50 ml. of concentrated ammonium hydroxide and acidification with acetic acid. The orange needles (1.78 g., 66%) have no melting point and are insoluble in water and organic solvents. The product was purified once more in the same manner for analysis.

Anal. Calcd. for $C_8H_7N_3OS$: C, 49.7; H, 3.6; S, 16.5. Found: C,49.5; H, 3.6; S, 16.5.

4-Anilino-2-ethylmercaptopyrimidine Hydrochloride.—Two grams of 2-thiol-4-anilinopyrimidine was refluxed with 5 ml. of 2 *N* sodium hydroxide solution and 1.6 g. of ethyl iodide in 100 ml. of ethanol. The alcohol was evaporated on the steam-bath, the residual aqueous solution extracted with ether, and the ethereal solution dried over sodium sulfate. After removal of the ether on the steam-bath, the colorless oil (2 g.) was converted to its hydrochloride with alcoholic hydrogen chloride. The hydrochloride, after recrystallization from ethanol containing hydrogen chloride, melted at 196–197° with effervescence (lit. 198°).[17]

4-Anilino-2-carboxymethylthiolpyrimidine.—Five grams of 4-anilino-2-thiolpyrimidine and 3 g. of chloroacetic acid were heated in 20 ml. of water until solution was complete. On cooling, the 4-anilino-2-carboxymethylthiolpyrimidine separated in almost quantitative yield. It was recrystallized from ethanol, forming needles, m. p. 197° (dec.).

Anal. Calcd. for $C_{12}H_{11}N_3O_2S$: C, 55.2; H, 4.2. Found: C, 54.9; H, 4.1.

4-Anilino-2-hydroxypyrimidine (N-Phenylcytosine).—One gram of 4-anilino-2-carboxymethylthiopyrimidine was refluxed with 15 ml. of concentrated hydrochloric acid for two hours. When the solution was made alkaline with ammonium hydroxide crystals separated (0.7 g.) which, on recrystallization from ethanol, formed colorless plates, m. p. 272–274° (dec.). Wheeler and Bristol[17] describe the material as plates melting "about 269°."

Anal. Calcd. for $C_{10}H_9N_3O$: N, 22.3. Found: N, 21.9.

4-Anilinopyrimidine.—One gram of 4-anilino-2-carboxymethylthiopyrimidine was refluxed with 3 g. of Raney nickel and 0.2 g. of sodium carbonate in 50 ml. of ethanol for three hours. The nickel was removed by filtration and the filtrate evaporated to a small volume on the steam-

(17) Wheeler and Bristol, *Am. Chem. J.*, **33**, 458 (1905).

(18) Polonovski, Pesson and Schmitt, *Bull. soc. chim.*, 392 (1948).

bath. The 4-anilinopyrimidine (0.6 g.) was precipitated with water and recrystallized from aqueous alcohol, m. p. 143–144° (lit. 142–143°).[19]

Acknowledgment.—We are indebted to Samuel W. Blackman for the microanalyses reported here.

Summary

2,4-Dithiolpyrimidine derivatives react with ammonia and a wide variety of amines with replacement of one thiol group by the amine. The 4-amino-2-thiol derivative is the first product in every instance. Substituents in the 5-position of the pyrimidine nucleus serve to block the reaction with secondary amines and certain highly hindered primary amines.

(19) Winklemann, *J. prakt. Chem.*, [2] **115**, 292 (1927).

TUCKAHOE 7, NEW YORK RECEIVED FEBRUARY 23, 1949

[CONTRIBUTION FROM THE BAKER LABORATORY OF CHEMISTRY AT CORNELL UNIVERSITY]

The Hydrolysis of Amino Groups in Certain 2,4,5,6-Tetrasubstituted Pyrimidines[1]

BY E. C. TAYLOR, JR., AND C. K. CAIN

Previous work has demonstrated that there is a variation in the lability toward hydrolysis of amino groups in different positions on a pyrimidine ring. For example, a 4-(or 6)-iminobarbituric acid containing hydrogen or alkyl groups in the 5-position may be readily converted to the corresponding barbituric acid by acid hydrolysis.[2a,b,c,d] Both imino groups of 2,4-diimino-5,5-dialkylbarbituric acids may be replaced by hydroxyl groups upon boiling with dilute acid, although the 4-amino group is more easily removed than the 2-amino group.[2d]

Amino groups in the 2-, 4-, 5- and 6-positions of the pyrimidine ring are potentially capable of existing in either the amino or the imino form. Since it is recognized that the double link C=N, as in the imines, the Schiff bases and the anils, is much less stable toward hydrolysis than the single link C–N,[3] the relative lability toward hydrolysis of the amino groups in various positions of the pyrimidine ring might indicate whether they exist in the amino or the imino form and thus might give information as to the structure of the molecule as a whole.

We have found that amino groups in the 4- and/or 6-positions of several 5-nitrosopyrimidines containing a hydroxyl group in the 2-position may be replaced readily by hydroxyl groups upon boiling the compound for a short time with 6 *N* hydrochloric acid. An amino group in the 2-position of such compounds is not removed under these mild conditions; prolonged heating with acid results instead in ring cleavage as shown by the isolation of guanidine from the reaction mixture. This behavior is of particular interest since the corresponding 2-hydroxy compounds are not affected under these more strenuous conditions.

Davidson and Epstein[4] reported the conversion of 5-amino-2,4,6-trihydroxypyrimidine into 2,4,5,6-tetrahydroxypyrimidine (dialuric acid), a reaction involving the hydrolysis of a 5-amino group in a 2,4,5,6-tetrasubstituted pyrimidine. We have found that the conditions necessary for this reaction are more strenuous than those necessary for the hydrolysis of the 4- and/or 6-amino groups in the compounds mentioned above. Again, substitution of an amino group for the 2-hydroxyl group changes the properties of the molecule; 2,5-di-

TABLE I

REACTION OF AMINOPYRIMIDINES WITH BOILING 6 *N* HYDROCHLORIC ACID

Starting material pyrimidine	Time, min.	Product	Yield, %
6-Amino-2,4-dihydroxy-5-nitroso-(I)	10	2,4,6-Trihydroxy-5-nitrosopyrimidine (III)	86
(I)	30	2,4,6-Trihydroxy-5-nitrosopyrimidene (III)	..
4,6-Diamino-2-hydroxy-5-nitroso- (II)	10	2,4,6-Trihydroxy-5-nitrosopyrimidine (III)	59
(II)	30	2,4,6-Trihydroxy-5-nitrosopyrimidine (III)	..
2,6-Diamino-4-hydroxy-5-nitroso- (VI)	10	2-Amino-4,6-dihydroxy-5-nitrosopyrimidine (VIII)	66
(VI)	30	Guanidine	..
2,4,6-Triamino-5-nitroso- (VII)	10	2-Amino-4,6-dihydroxy-5-nitrosopyrimidine (VIII)	67
(VII)	30	Guanidine	..
2,4,6-Trihydroxy-5-nitroso- (III)	120	No reaction	
2-Amino-4,6-dihydroxy-5-nitroso- (VIII)	30	Guanidine	
5-Amino-2,4,6-trihydroxy- (IV)	30	2,4,5,6-Tetrahydroxypyrimidine (V)	55
2,5-Diamino-4,6-dihydroxy- (IX)	30	Guanidine	
5-Acetamido-2-amino-4,6-dihydroxy- (X)	2	2,5-Diamino-4,6-dihydroxypyrimidine (IX)	86.5
(X)	30	Guanidine	..
5,6-Diamino-2,4-dihydroxy-	60	No reaction	
4,5,6-Triamino-2-hydroxy-	60	No reaction	
2,5,6-Triamino-4-hydroxy-	60	No reaction	
2,4,5,6-Tetramino-	60	No reaction	

(1) The investigations described in this paper were undertaken in collaboration with the Office of Naval Research, Navy Department, Washington, D. C., and were aided by a grant to Cornell University by The Nutrition Foundation, Inc., New York City. They represent a part of a collaborative project on "Newer Members of the B Group of Vitamins."

(2) (a) Conrad, *Ann.*, **340**, 310 (1905); (b) Tabern and Volwiler, THIS JOURNAL, **56**, 1139 (1934); (c) Chamberlain, *et al.*, *ibid.*, **57**, 352 (1935); (d) Cope and Hancock, *ibid.*, **61**, 776 (1939).

(3) Sidgwick, "The Organic Chemistry of Nitrogen," new ed. rev. by Taylor and Baker, Oxford University Press, New York, N. Y., 1937, p. xv.

(4) Davidson and Epstein, *J. Org. Chem.*, **1**, 305 (1936).