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).

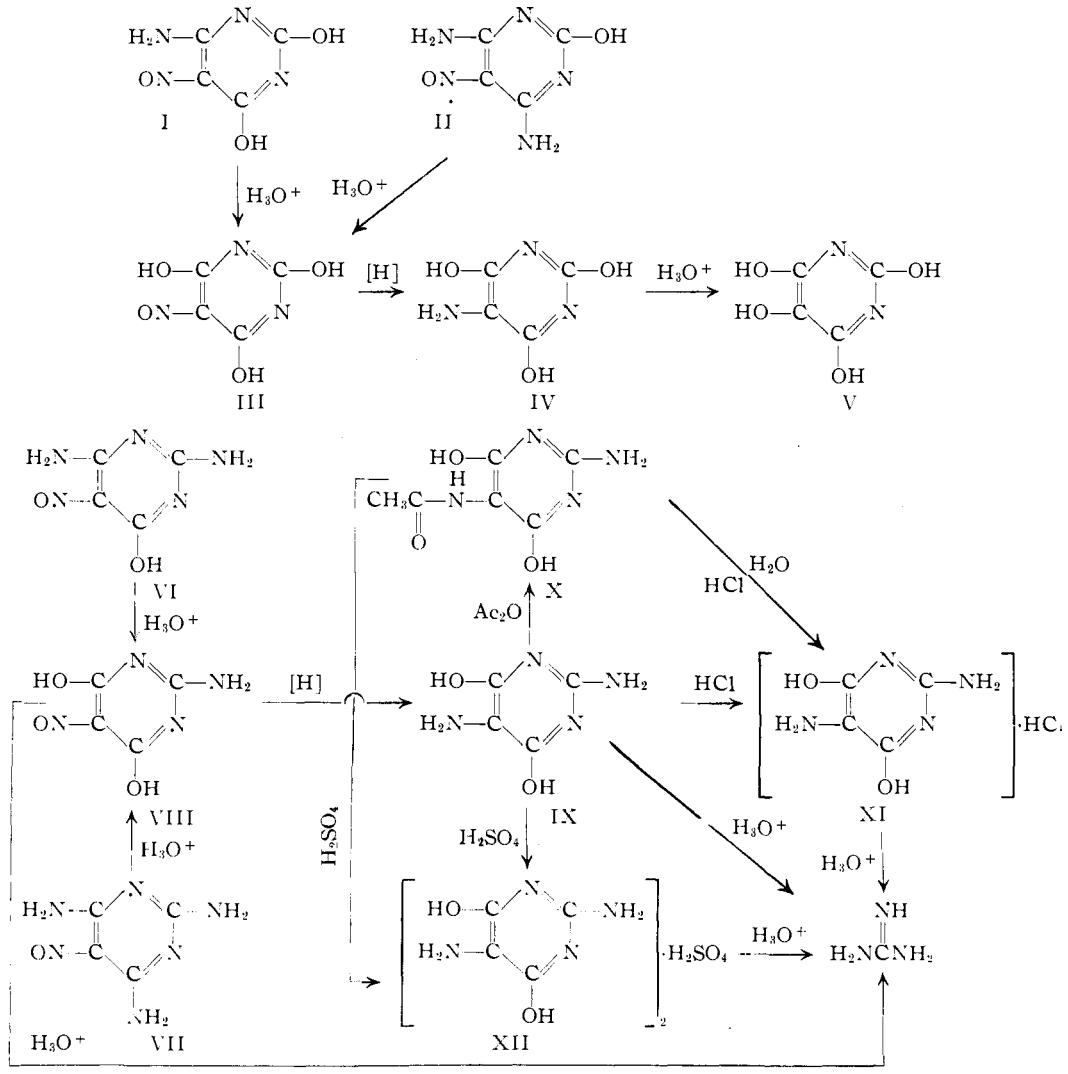


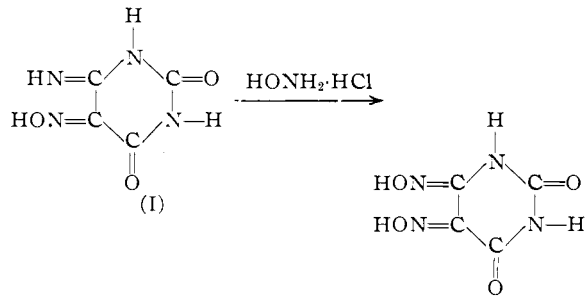
Fig. 1.

amino-4,6-dihydroxypyrimidine undergoes ring cleavage upon prolonged heating in acid solution without detectable formation of any compound resulting from hydrolysis of either the 2- or 5-amino group.

In contrast to these results, 5,6-diamino-2,4-dihydroxypyrimidine, 4,5,6-triamino-2-hydroxypyrimidine, 2,5,6-triamino-4-hydroxypyrimidine and 2,4,5,6-tetraminopyrimidine were recovered unchanged after long boiling with 6 *N* hydrochloric acid. Hence, it would appear that the presence of amino groups in both the 5- and 6-positions not only prevents the hydrolysis of any amino group but stabilizes the entire pyrimidine ring as well.

The essential reactions involved in these experiments are summarized in Fig. 1; the reaction conditions and results are shown in Table I.

Although there is insufficient evidence to allow a definite conclusion as to the tautomeric forms exhibited by the various amino groups considered, one is tempted to conclude that at least the 4- and 6-amino groups of the 5-nitrosopyrimidines herein described probably exist predominantly in the imino rather than the amino form. An interesting experiment that might relate to this conclusion is the smooth conversion of 6-amino-2,4-dihydroxy-5-nitrosopyrimidine (I) into alloxan-5,6-dioxime by refluxing with hydroxylamine hydrochloride in absolute alcohol.



At least, it may be concluded that this 6-imino (or amino) group possesses greater reactivity toward this reagent than does the corresponding oxo (or hydroxyl) group; that is, 2,4,6-trihydroxy-5-nitrosopyrimidine (III) is not converted to alloxan-5,6-dioxime under the same conditions.

Similarly, the 5-amino group of 5-amino-2,4,6-trihydroxypyrimidine is probably predominantly in the amino form. This latter conclusion is confirmed by the observation that the 5-amino group of this compound may be readily acetylated or diazotized.

The resistance toward acid hydrolysis of an amino group in the 2-position of a pyrimidine ring might indicate that it exists predominantly in the amino rather than in the imino form. An alternative explanation might be related to the fact that the 2-aminopyrimidines are derived from guanidine which is known to be considerably more stabilized by resonance in acid solution than is urea from which the 2-hydroxypyrimidines are derived.

Experimental

Hydrolysis of 4- and 6-Amino Groups of 5-Nitrosopyrimidines.—The following procedure was used for conversions I → III, II → III, VI → VIII and VII → VIII (Fig. 1).

A suspension of 5.0 g. of the appropriate pyrimidine in 80 ml. of 6 *N* hydrochloric acid was boiled for ten to fifteen minutes. The clear yellow solution was treated with Norit, filtered and the filtrate adjusted to *p*H 10 with ammonium hydroxide. After cooling to 0° the precipitated ammonium salt was collected by filtration and washed with cold water followed by acetone. Recrystallization from water gave the free pyrimidine, from 0.1 *N* ammonium hydroxide gave the monoammonium salt or from 1 *N* ammonium hydroxide gave the diammonium salt. Identification of violuric acid (III) and its ammonium salts or iminovioluric acid (VIII)[5] and its ammonium salts was accomplished by analyses and by a comparison of ultraviolet absorption spectra and melting points with those of authentic samples.

Isolation of Guanidine as a Product of Ring Cleavage.—The following procedure was used to establish cleavage of the pyrimidine ring of Compounds VIII, IX, XI and XII in Fig. 1.

A suspension of 2 g. of the pyrimidine in 20 ml. of 6 *N* hydrochloric acid (or 7.5 *N* sulfuric acid) was refluxed for one-half hour. After treatment of the resulting clear red solution with Norit, filtering and neutralizing with ammonium hydroxide, 10 ml. of a saturated aqueous solution of picric acid was added. The resulting precipitate of guanidine picrate was collected by filtration after cooling to 0°. In every case, a mixed melting point with an authentic sample of guanidine picrate showed no depression.

Hydrolysis of 5-Amino-2,4,6-trihydroxypyrimidine (IV).—A suspension of 0.5 g. of 5-amino-2,4,6-trihydroxypyrimidine in 10 ml. of 6 *N* hydrochloric acid was refluxed for thirty minutes and then filtered from the unreacted starting material (0.21 g.). Upon cooling the filtrate to 0°, 0.16 g. (55%) of large yellow crystals of 2,4,5,6-tetrahydroxypyrimidine (dialuric acid, V) separated; m. p. 214° (uncor.).

2,5-Diamino-4,6-dihydroxypyrimidine (IX).—A solution of 1.0 g. of the ammonium salt of 2-amino-4,6-dihydroxy-5-nitrosopyrimidine (VIII) in 100 ml. of boiling water was treated with sodium hydrosulfite until a clear yellow solution resulted. The hot solution was treated immediately with Norit and filtered into a preheated flask. On cooling, 0.8 g. (97%) of small glistening plates separated.

5-Acetamido-2-amino-4,6-dihydroxypyrimidine (X).—A suspension of 0.55 g. of 2,5-diamino-4,6-dihydroxypyrimidine (IX) in 12 ml. of acetic anhydride was refluxed for one-half hour. Boiling water (50 ml.) was added and the resulting clear orange solution was treated with Norit, filtered and cooled to yield 0.325 g. of fine, silky crystals. An additional 0.16 g. was obtained by concentrating the filtrate; total yield 68%. The product was purified by recrystallization from water. The long colorless needles decomposed slowly upon heating above 300°.

Anal. Calcd. for $C_6H_8N_4O_3$: N, 30.4. Found: N, 30.5.

Alloxan-5,6-dioxime.—A suspension of 1.0 g. of 6-amino-2,4-dihydroxy-5-nitrosopyrimidine (I) and 10 g. of hydroxylamine hydrochloride in 50 ml. of absolute ethanol was refluxed for three hours during which time the color of the suspended solid gradually changed from a rose-red to a light yellow. The yellow solid was collected by filtration of the hot reaction mixture and washed thoroughly with boiling water to give 0.78 g. (71%) of light yellow microcrystals melting at 242° (uncor.) in good agreement with the reported value.[6]

Summary

1. The lability toward hydrolysis in acid solution of the amino groups in certain 2,4,5,6-tetrasubstituted pyrimidines has been studied.

2. Amino groups in the 4- and/or 6-positions of 5-nitrosopyrimidines containing an amino or hydroxyl group in the 2-position may be readily replaced by hydroxyl groups by short boiling with dilute acid.

3. In two instances, the substitution of an amino for a hydroxyl group in the 2-position of the pyrimidine ring has resulted in instability of the nucleus toward acid hydrolysis as shown by the isolation of guanidine as a product of ring cleavage.

4. The presence of amino groups in both the 5- and 6-positions of a pyrimidine ring not only prevents the hydrolysis of any amino group but also stabilizes the pyrimidine ring toward hydrolytic cleavage.

5. 6-Amino-2,4-dihydroxy-5-nitrosopyrimidine has been smoothly converted into alloxan-5,6-dioxime by refluxing with hydroxylamine in absolute ethanol.

ITHACA, NEW YORK RECEIVED DECEMBER 6, 1948

(5) Traube, *Ber.*, **26**, 2551 (1893).

(6) Davidson and Bogert, *Proc. Natl. Acad. Sci.*, **18**, 490 (1932).