of the order of increasing ionization constants but is the same as the order of decreasing bulkiness of the groups attached to the nitrogen atom.

A similar situation has been described by H. C. Brown and his collaborators[14] for the equilibrium of the reaction of aliphatic and pyridine bases with trimethylboron, in which this steric hindrance has been termed "F-Strain." The present case seems to be somewhat different in that here the rate of reaction of a base with a weak acid is found to be subject to steric hindrance, suggesting that in the transition complex it must be necessary for the amine to approach the weak acid very closely to pull off a proton. If such is the case one would expect the steric hindrance in the acid to affect the rate also. This is borne out by the lower rates observed for α-acetamidophenylacetic acid, especially with sterically hindered catalysts, as well as by the results of preliminary studies on other acylamino acids, tabulated in Table V.

TABLE V

EFFECT OF STRUCTURE OF ACYLAMINO ACID ON RATE OF PYRIDINE CATALYZED REACTION WITH ACETIC ANHYDRIDE

Compound	Relative rate
Benzoylalanine	3.7
α-Benzamidophenylacetic acid	1.6
α-Acetamidophenylacetic acid	1.4
Benzoylphenylalanine	1

It is found that the reaction rate decreases as the size of the group on the α-carbon in the acylamino acid increases.

It thus seems plausible that the better yields of acylaminoketone obtained when 2-picoline and 1-methylpiperidine are used as catalysts are due to the more rapid formation of the conjugate base of an azlactone intermediate,[6] thereby decreasing the amount of decomposition of the azlactone in other ways. The use of 4-picoline as a catalyst deserves comment, for in this case the yield was about the same as for the pyridine-catalyzed reaction, although the rate of carbon dioxide evolution was much greater. It is probable that condensation of the ketonic product with the active methyl group of 4-picoline occurs.

A further study of the mechanism of the Dakin–West reaction is in progress.

Summary

1. The reaction rate constants for the Dakin–West reaction of several acylamino acids with several anhydrides have been measured at 100° by measuring the rate of evolution of carbon dioxide. The reaction is first order with respect to both the acylamino acid and the basic catalyst.

2. The reaction is catalyzed by tertiary amines of both the aliphatic and the pyridine series. The catalytic activity of these bases is found to depend more upon steric factors than electronic factors. 3-Picoline and 1-methylpiperidine were found to be somewhat better catalysts for the reaction than pyridine.

URBANA, ILLINOIS RECEIVED DECEMBER 14, 1949

(14) Brown, Schlessinger and Cardon, THIS JOURNAL, **64**, 325 (1942); Brown and Seyishi, *ibid.*, **70**, 2878 (1948).

[CONTRIBUTION FROM THE WELLCOME RESEARCH LABORATORIES]

Studies on Condensed Pyrimidine Systems. IV.[1] Some Thiazolo[5,4-d]pyrimidines

BY ELVIRA A. FALCO AND GEORGE H. HITCHINGS

The observation that antimicrobial action (against *Lactobacillus casei*) is a general property of certain functional derivatives of condensed pyrimidine systems[2,3] indicates the desirability of study of such derivatives whenever they become accessible. During studies on the reaction of pyrimidine derivatives with phosphorus pentasulfide[4,5] the preparation of 5-thiobenzamido-2,4-diaminopyrimidine from the benzamide (I) was attempted. A crystalline product was obtained; however, analysis indicated that although the desired exchange of sulfur for oxygen had taken place, this process had been accompanied by the loss of the elements of ammonia. The product, therefore, appeared to be 5-amino-2-phenylthiazolo[5,4-d]pyrimidine (II). A study of this type of reaction indicates it to be quite generally applicable to the synthesis of 2-substituted-5-amino-, 5,7-diamino- and 5,7-dithiolthiazolo-[5,4-d]pyrimidines, types of functional derivative desired for microbiological study.[2]

Confirmation of the structure of these new substances was sought through the preparation of some members of the series by a known route. The methods employed in Heilbron's laboratory[6,7,8] did not appear to be adaptable to the synthesis of the desired derivatives. However, 2-methyl-5,7-dihydroxythiazolo[5,4-d]pyrimidine (III, R = CH_3) had been prepared by treatment of thiouramil IV with acetic anhydride, followed

(1) Previous papers in this series (unnumbered) deal with pteridines, THIS JOURNAL, **69**, 2553 (1947); **72**, 78 (1950); and *p*-oxazino-(2,3-d)pyrimidines, *ibid.*, **71**, 474 (1949).

(2) Hitchings, Elion, VanderWerff and Falco, *J. Biol. Chem.*, **174**, 765 (1948).

(3) Hitchings, Elion, Falco, Russell, Sherwood and VanderWerff, *ibid.*, **183**, 1 (1950).

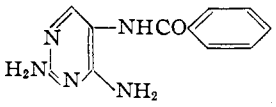
(4) Elion and Hitchings, THIS JOURNAL, **69**, 2138 (1947).

(5) Russell, Elion, Falco and Hitchings, *ibid.*, **71**, 2279 (1949).

(6) Cook, Heilbron, Macdonald and Mahadevan, *J. Chem. Soc.*, 1064 (1949).

(7) Cook, Downer and Heilbron, *ibid.*, 1069 (1949).

(8) Cook, Davis, Heilbron and Thomas, *ibid.*, 1071 (1949).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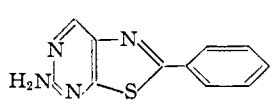
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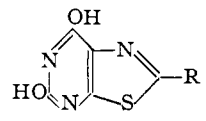
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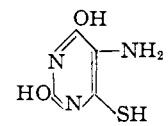
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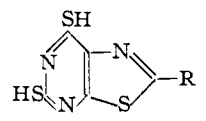
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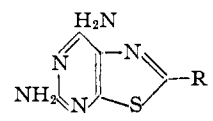
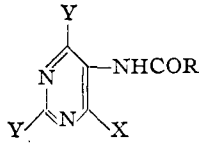
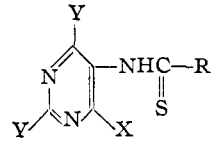

VI

by removal of the N-acetyl groups.[9,10] This substance appeared to be attainable by the new method. 5-Acetamido-2,4,6-trihydroxypyrimidine gave the dithiol derivative (V, R = CH_3) which was, however, extremely resistant to hydrolysis. In a similar manner the diamino compound (VI, R = CH_3) was obtained without difficulty, but, although an aminohydroxy derivative was obtained from it, the hydrolysis of this to the dihydroxy derivative was unfruitful. This general scheme, however, was successful when applied to the 2-phenyl derivatives. 5,7-Dihydroxy-2-phenylthiazolo[5,4-d]pyrimidine (III, R = C_6H_5) was synthesized *via* the benzoylation of thiouramil and the same substance was obtained by way of the phosphorus pentasulfide method, through the deamination of 5,7-diamino-2-phenylthiazolo[5,4-d]pyrimidine.

The mechanism of the reaction involved in the synthesis described here is of some interest but a definitive answer to this problem cannot be given at this time. It appears likely that the first step consists in the formation of the thioamide (A).


(X = OH, NH_2)
(Y = OH, NH_2, H)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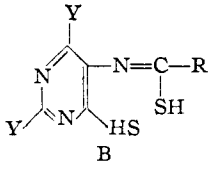
B

Replacement of an amino or hydroxyl group by thiol on the pyrimidine nucleus would give the thioamidothiolpyrimidine (B) which would be converted to the thiazole by elimination of hydrogen sulfide. The replacement of hydroxyl by thiol groups in the pyrimidine series is well known[4,5]; however, the replacement of amino by thiol groups, and the isolation of the intermediate thioamide have not yet been demonstrated unequivocally.

The results of microbiological studies of these substances will be presented elsewhere.

TABLE I

ULTRAVIOLET SPECTRA OF SUBSTITUTED THIAZOLE[5,4-d]-PYRIMIDINES

	pH 1				pH 11			
	Maxima		Minima		Maxima		Minima	
Substituents	Ω, mμ	E_m	Ω, mμ	E_m	Ω, mμ	E_m	Ω, mμ	E_m
5,7-Diamino-2-phenyl-	315	23,000	260	4000	232 330	21,900 18,200	270	3640
5,7-Dihydroxy-2-phenyl-	300	19,400	250	3180	330	20,100	265	2820
2-*p*-Chlorophenyl-5,7-diamino-	320	24,200	265	4680	238 335	13,200 16,000	278	4400
5,7-Diamino-2-methyl-	265	12,700	250	9150	280	13,000	250	4320
5,7-Dihydroxy-2-methyl-	255	9,800			275 293	10,600 10,200	235 285	2740 9800
5,7-Dithiol-2-methyl-	305 350	22,700 7,500	250	4740	295 370	15,700 6,450	250 350	6020 5900

Experimental

5-Benzamidopyrimidines.—The method employed was essentially the same as that reported by Wilson.[11] The hitherto unreported amides are listed below:

5-Benzamido-2,4-diaminopyrimidine.—Yield 86%, m. p. 213–214° (dec.). *Anal.* Calcd. for $C_{11}H_{11}N_5O \cdot {}^1/_2H_2O$: N, 29.4. Found: N, 29.3.

Hydrochloride.—Calcd. for $C_{11}H_{11}N_5O \cdot HCl$: C, 49.7; H, 4.5; N, 26.3. Found: C, 49.2; H, 4.8; N, 26.1.

5-Benzamido-2,4,6-triaminopyrimidine.—Yield 42%, m. p. 274–275°. *Anal.* Calcd. for $C_{11}H_{12}N_6O$: C, 54.1; H, 5.0; N, 34.4. Found: C, 54.1; H, 5.0; N, 34.2.

5-*p*-Chlorobenzamido-2,4-diamino-6-hydroxypyrimidine.—Yield 65%, m. p. 345–348° (dec.). *Anal.* Calcd. for $C_{11}H_{10}ClN_5O_2$: N, 25.3. Found: N, 25.3.

Thiazolo[5,4-d]pyrimidines from 5-Acylaminopyrimidines. General Method.—The 5-amidopyrimidine and 3 parts by weight of phosphorus pentasulfide are suspended in about 10 volumes of tetralin and heated, with stirring, at 150–200° for two hours. The reaction mixture is cooled and filtered. The insoluble material is washed with ether and then leached with warm 1–2 *N* ammonium hydroxide. The residue is recrystallized from absolute alcohol.

5-Amino-2-phenylthiazolo[5,4-d]pyrimidine.—This compound was prepared from 5-benzamido-2,4-diaminopyrimidine by the above given general method at a temperature of 160–200°. The yellow plates melted at 285–287°; yield 31%. *Anal.* Calcd. for $C_{11}H_8N_4S$: C, 57.9; H, 3.5; N, 24.6. Found: C, 58.2; H, 3.4; N, 24.5.

5,7-Diamino-2-phenylthiazolo[5,4-d]pyrimidine.—5-Benzamido-2,4,6-triaminopyrimidine was treated with phosphorus pentasulfide at 180–200°, giving yellow plates melting at 279–281°; yield 27%. In one experiment, the reaction did not take place at 150°. The same compound was obtained from 5-benzamido-2,4-diamino-6-hydroxypyrimidine[11] at 150–160°. The pale yellow prisms melted at 277–278°; yield 65%. The products from the two starting materials gave identical ultraviolet absorption spectra. A mixture of the two products melted at 277–278°. *Anal.* Calcd. for $C_{11}H_9N_5S$: C, 54.8; H, 3.7; N, 28.8; S, 13.1. Found: C, 54.4; H, 3.7; N, 28.8; S, 12.6.

5,7-Diamino-2-methylthiazolo[5,4-d]pyrimidine was prepared from 5-acetamido-2,4-diamino-6-hydroxypyrimidine[12] at 180–200°. The yellow plates melted at

(9) Fischer and Ach, *Ann.*, **288**, 166 (1895).
(10) Weidel and Niemilowicz, *Monatsh.*, **16**, 721 (1895).
(11) W. Wilson, *J. Chem. Soc.*, 1157 (1948).
(12) Traube, Schottländer, Goslich, Peter, Meyer, Schlüter, Steinbach and Bredow, *Ann.*, **432**, 266 (1923).

246–250°; yield 50%. *Anal.* Calcd. for $C_6H_7N_5S$: C, 39.8; H, 3.9; N, 35.2. Found: C, 39.7; H, 3.4; N, 35.2.

5,7-Dithiol-2-methylthiazolo[5,4-d]pyrimidine was prepared at 150° from 5-acetamido-2,4,6-trihydroxypyrimidine,[13] giving long orange needles melting at 298°; yield 8%. *Anal.* Calcd. for $C_6H_5N_3S_3$: C, 33.5; H, 2.3; N, 19.5. Found: C, 33.7; H, 2.4; N, 19.4.

2-*p*-Chlorophenyl-5,7-diaminothiazolo[5,4-d]pyrimidine was prepared from 5-*p*-chlorobenzamido-2,4-diamino-6-hydroxypyrimidine at 180°. The yield of yellow needles, m. p. 297–299°, was 76%. *Anal.* Calcd. for $C_{11}H_8ClN_5S$: N, 25.3. Found: N, 25.4.

Deamination of 5,7-Diamino-2-methylthiazolo[5,4-d]-pyrimidine.—One gram of 5,7-diamino-2-methylthiazolo-[5,4-d]pyrimidine was dissolved in 65 ml. of 0.5 *N* hydrochloric acid and a solution of 0.5 g. of sodium nitrite in 10 ml. of water was added in small portions over thirty minutes. The solution was warmed on the steam-bath for one hour and then neutralized with ammonium hydroxide. The precipitate was collected, and recrystallized by solution in dilute alkali and precipitation with dilute acetic acid. A white powder is formed which decomposes at about 320°. One amino group was replaced by an hydroxyl by this procedure. *Anal.* Calcd. for $C_6H_6N_4OS$: N, 30.8. Found: N, 30.6.

Dibenzoyl Derivative of 5,7-Dihydroxy-2-phenylthiazolo[5,4-d]pyrimidine.—One gram of the ammonium salt of thiouramil[9,10] was refluxed with 50 ml. of benzoyl chloride for two hours. The benzoyl chloride was removed *in vacuo*, and the residue was leached with 25 ml. of 50% ethanol, washed several times with ether and then recrystallized from ethyl acetate. The compound was obtained as colorless needles, m. p. 240°. The yield was 1.25 g. (50%). *Anal.* Calcd. for $C_{25}H_{17}N_3O_4S$: C, 66.0; H, 3.7; N, 9.3. Found: C, 66.4; H, 3.8; N, 9.7.

5,7-Dihydroxy-2-phenylthiazolo[5,4-d]pyrimidine. A. From the Dibenzoyl Derivative.—One-half gram of the above dibenzoyl derivative was boiled with 50 ml. of 1 *N* sodium hydroxide solution until it had dissolved completely. The solution was neutralized with acetic acid; the precipitate was collected, washed with ethanol and ether and recrystallized by solution in aqueous alkali and precipitation with acetic acid. The compound is a white powder which does not melt at 340°. Benzoic acid was recovered from the filtrate. *Anal.* Calcd. for $C_{11}H_7N_3O_2S$: N, 17.2. Found: N, 17.2.

(13) Piloty and Finckl, *Ann.*, **333**, 85 (1904).

B. By Deamination of 5,7-Diamino-2-phenylthiazolo-[5,4-d]pyrimidine.—To 0.6 g. of 5,7-diamino-2-phenylthiazolo[5,4-d]pyrimidine were added 5 ml. of 10 *N* sulfuric acid and 1 g. of sodium nitrite dissolved in 5 ml. of water. The mixture was warmed on the steam-bath for one hour and then neutralized with ammonium hydroxide. The precipitate was recrystallized from ethanol and formed yellow plates which do not melt at 330°. The above compound (0.18 g.) was heated with 50 ml. of 6 *N* hydrochloric acid in a bomb at 140° for sixteen hours. The solution was evaporated to dryness on the steam-bath and the residue was taken up in dilute alkali and precipitated with dilute acetic acid. The resulting compound does not melt at 340°. It has an ultraviolet absorption spectrum identical with that of the compound obtained by saponification of the dibenzoyl derivative. *Anal.* Calcd. for $C_{11}H_7N_3O_2S$: C, 53.8; H, 2.9; N, 17.2. Found: C, 53.6; H, 2.8; N, 17.3.

5,7-Dihydroxy-2-methylthiazolo[5,4-d]pyrimidine.—This compound was prepared by refluxing 1.0 g. of the ammonium salt of thiouramil with 30 ml. of acetic anhydride.[9,10] After recrystallization from water, the compound was dried at 140°. It did not melt at 340°.[14] *Anal.* Calcd. for $C_6H_5N_3O_2S$: C, 39.4; H, 2.7; N, 22.9. Found: C, 39.7; H, 2.6; N, 22.9.

Ultraviolet Absorption Spectra.—The spectra were measured with a Beckman spectrophotometer. For solutions of *p*H 1, 0.1 *N* hydrochloric acid was used and for *p*H 11, a glycine–sodium hydroxide buffer.

Acknowledgment.—We are indebted to Samuel W. Blackman and Nicholas M. Martinez, Jr., for microanalyses reported here.

Summary

Several 5-amino-, 5,7-diamino- and 5,7-dithiolthiazolo[5,4-d]pyrimidines, substituted in the 2-position by methyl or phenyl, have been synthesized by the reaction of 5-acetamido(and benzamido)-4-hydroxy(or amino)-pyrimidines with phosphorus pentasulfide.

(14) Fischer and Ach[9] give a melting point of 220–221° while Weidel and Niemilowicz[11] state that the compound does not melt above 300°. The method of preparation employed by the two authors and the other properties of the products are essentially identical and in agreement with the present observations.

TUCKAHOE 7, N. Y. RECEIVED DECEMBER 13, 1949

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, QUEEN'S UNIVERSITY, AND THE RESEARCH AND BIOLOGICAL LABORATORIES, AYERST, MCKENNA AND HARRISON, LTD., MONTREAL]

The Reaction of Amines with 2-Nitramino-1,3-diaza-2-cycloalkenes

BY A. F. MCKAY,[1] J. R. COLEMAN AND GORDON A. GRANT

Primary amines have been shown[2] to combine with 2-nitramino-1,3-diaza-2-cycloalkenes I to give 2-alkylamino- or 2-aralkylamino-1,3-diaza-2-cycloalkenes II. The picrates of several of these 1,3-diaza-2-cycloalkenes are described in Table I.

It was previously[2] noted that water liberated during this reaction was responsible for the formation of cyclic ureas as side products. The cyclic ureas were thought to form almost exclusively from the action of water on the 2-substituted amino-1,3-diaza-2-cycloalkenes. Further work on this reaction has shown that 2-nitramino-1,3-diaza-2-cycloalkenes are hydrolyzed almost quantitatively to the corresponding cyclic ureas by refluxing with excess water containing a low concentration of an amine, *e. g.*, benzylamine. The following cyclic ureas were prepared in this manner, the yields are given in parentheses: 4-hydroxy-2,6-diaza-1-cyclohexanone (98), *m. p.* 210–211°[3]; 2,6-diaza-1-cyclohexanone (98), *m. p.* 265–266°[2,4,5]; 3-methyl-2,6-diaza-1-cyclohexanone

(1) Defense Research Chemical Laboratories, Ottawa, Ontario.

(2) A. F. McKay, M. N. Buchanan and Gordon A. Grant, THIS JOURNAL, **71**, 766 (1949).

(3) J. Tafel and L. Reindl, *Ber.*, **34**, 3289 (1901), reported a melting point of 185–195°.

(4) E. Fischer and H. Koch, *Ann.*, **232**, 224 (1886).

(5) A. P. N. Franchimont and H. Friedmann, *Rec. trav. chim.*, **26**, 218 (1907).