Anal. Calcd. for $C_{16}H_{11}O_3Br$: C, 58.0; H, 3.3. Found: C, 58.0; H, 3.7.

Proof of Structure.—A methyl alcoholic solution containing 4 g. of the triketone and 1.5 g. of 30% hydrogen peroxide was cooled to 0° and treated gradually with 1 g. of potassium hydroxide in the same solvent. The resulting red solution was left to itself until most of the color had disappeared, then acidified and extracted with ether. The oily residue left after the ether had been evaporated was digested for a short time on a steam-bath with sulfuric acid in order to decompose intermediate products, then subjected to the usual treatment for the separation of the acid and the neutral products. The neutral fraction contained only *p*-bromoacetophenone—identified as benzal *p*-bromoacetophenone. The acid fraction contained *p*-bromobenzoic acid and benzoic acid—separated by crystallization and identified by melting points. The yields were: 30% of the possible quantity of bromoacetophenone, 60% of bromobenzoic acid and 92% of benzoic acid.

2-Methoxy-2-*p*-bromophenyl-5-phenyl Furanone-3.—The second ether that was formed when the mixture of the triketones was alkylated, was obtained by concentrating the solution under diminished pressure. It crystallized from methyl alcohol in fine needles melting at 102°.

Anal. Calcd. for $C_{17}H_{13}O_3Br$: C, 59.1; H, 3.8. Found: C, 59.0; H, 4.0.

Ozonization.—The same procedure that was employed in the case of the isomeric ether resulted in methyl *p*-bromobenzoate melting at 80° and identified by comparison with a sample on hand—and benzoic acid. The yields were, respectively, 60 and 75%.

Benzoyl Methyl-*p*-bromophenyl Diketone, X.—The triketone was obtained without difficulty by hydrolyzing the ether and isolating the product by means of the copper derivative. It crystallized in yellow plates melting at 88–90°.

Anal. Calcd. for $C_{16}H_{11}O_3Br$: C, 58.0; H, 3.5. Found: C, 57.8; H, 3.5.

Proof of Structure.—Oxidation with alkaline hydrogen peroxide in the manner described under the isomeric triketone gave *p*-bromobenzoic acid—85% of the possible quantity—benzoic acid and acetophenone (50%) which was identified as *m*-nitrobenzal acetophenone.

2-Acetoxy-2,5-diphenyl Furanone-3.—All methods of preparation—from the chloro compound, the ether or the triketone—gave the same product melting at 140°.

Anal. Calcd. for $C_{16}H_{10}O_3(COCH_3)$: C, 73.5; H, 4.9; $COCH_3$, 14.6. Found: C, 73.4; H, 4.8; $COCH_3$, 14.3.

Summary

The properties of β-hydroxyl derivative of 2,5-diphenylfuran are compared with those of the hydroxyl derivative of 2,4,5-triphenylfuran. The removal of the phenyl group in the 4-position does not affect the properties of the hydroxyl compound but it diminishes the stability of the furanone into which the hydroxyl compound passes by spontaneous ketonization.

CAMBRIDGE, MASS. RECEIVED AUGUST 5, 1936

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, YALE UNIVERSITY]

Researches on Pyrimidines. CLIV. Pyrimidine Side Chain Reactions Useful for the Synthesis of 1,3-Diazines Related Structurally to Vitamin B_1[1]

BY ANNE LITZINGER[2] AND TREAT B. JOHNSON

In two previous publications from this Laboratory,[3] the authors have emphasized the importance of increasing our present knowledge of aliphatic chemistry as applied to the pyrimidine cycle, and the bearing of such research developments on the determination of the correct constitution of vitamin B_1. In our preliminary paper entitled "Synthesis of Uracil-5-methylamine," we wrote as follows: "We believe that constructions of this type will prove to be of immediate interest in connection with the development of the newer chemistry of vitamin B_1."

The object of this paper is to present and describe a series of new reactions which have been applied successfully in our pyrimidine investigations, and which have opened up a practical method for synthesizing this interesting pyrimidine amine.[4] The chemistry of this amine will be discussed in the next paper of this series.[5]

The starting point of our new program of synthesis was the ethyl ester of 2-ethylmercapto-6-oxypyrimidine-5-acetic acid I which was first described by Johnson and Speh.[6] Applying suc-

(1) This research was partially supported by a special grant from the Research Committee of the American Medical Association.

(2) This paper was constructed from a thesis presented by Dr. Anne Litzinger in June, 1936, to the Graduate Faculty of Yale University in partial fulfilment of the requirements for the degree of Doctor of Philosophy.

(3) Pyrimidine paper CXLVI, Johnson and Litzinger, THIS JOURNAL, **57**, 1135 (1935); CLIII, Johnson and Litzinger, *Science* **84**, 25 (1936).

(4) Nomenclature: Uracil-5-methylamine or thyminylamine. The last name is coined to emphasize its aliphatic nature and to indicate its relationship to the naturally occurring pyrimidine-*thymine*.

(5) CLV, THIS JOURNAL, **58**, 1940 (1936).

(6) Johnson and Speh, *Am. Chem. J.*, **38**, 602 (1907).

cessfully the different basic reactions of the Curtius technique[7] for conversion of a carboxyl into an amino group with this pyrimidine I, we have succeeded in isolating in crystalline form all the intermediate products characteristic of the series of reactions involved in the introduction of an amino group. These intermediates are recorded in Table I. A description of several

TABLE I

INTERMEDIATES (PART ONE)

2-Ethylmercapto-6-oxypyrimidine-5-acetylhydrazide, II
2-Ethylmercapto-6-oxypyrimidine-5-acetylazide, III
2-Ethylmercapto-6-oxypyrimidine-5-methyl isocyanate, IV
Ethyl 2-ethylmercapto-6-oxypyrimidine-5-methylurethan IX
2-Ethylmercapto-6-oxypyrimidine-5-methylamine, VI

INTERMEDIATES (PART TWO)

Uracil-5-acetylhydrazide, XI
Uracil-5-acetylazide, XII
Uracil-5-methyl isocyanate or thyminyl isocyanate, XIII
Ethyl thyminyl-urethan, XV

other derivatives separated and identified in the course of the work is also given in the Experimental Part of this paper. We are extending this research to include the acetate derivatives of other types of pyrimidines, and characterized structurally by side chain substitutions in positions 2, 4 and 5 of the pyrimidine cycle.

Experimental Part

$\overline{NHC(SC_2H_5)=NHC=C(CH_2COOC_2H_5)CO}$. **Ethyl 2-ethylmercapto-6-oxypyrimidine-5-acetate,** I.—The starting material of the series of reactions leading up to the final synthesis of thyminylamine was this ethyl ester of 2-ethylmercapto-6-oxypyrimidine-5-acetic acid. This pyrimidine was obtained in the form of its sodium salt by condensing diethyl formylsuccinate with ethyl pseudothiourea, in alkaline solution, according to the procedure previously described in a paper from this Laboratory by Johnson and Speh.[6] This pyrimidine is formed in excellent yield, is easily purified by crystallization from 50% ethyl alcohol, and crystallizes from hot solutions as a beautiful fibrous mass of colorless needles.

$\overline{NHC(SC_2H_5)=NCH=C(CH_2CONHNH_2)CO}$. **2-Ethylmercapto-6-oxypyrimidine-5-acetylhydrazide. II.—Thirty** grams of the mercapto-pyrimidine acetate I (m. p. 146–147°) is dissolved in 300 ml. of absolute alcohol and to the hot solution is added 1.5 equivalents of 42% hydrazine hydrate (18 g.). The clear solution is then refluxed for two hours or until solid material begins to separate from the hot reaction mixture. Although the hydrazide is only moderately soluble in cold absolute alcohol, complete separation from solution is slow and, therefore, the reaction mixture is allowed to stand at room temperature for twenty-four hours before filtering off the crystalline hydrazide. This yields about 27 g. of the crude hydrazide melting at 198–200° with decomposition. On concentrating the alcohol filtrate more of the hydrazide is obtained contaminated with the unreacted pyrimidine acetate I. Such mixtures can be separated easily, however, by careful crystallization from absolute alcohol. Purification of the hydrazide is accomplished easily by recrystallization from 90% alcohol, and it crystallizes as sheaves of glistening plates which melt at 207–208° with decomposition. *Anal.* Calcd. for $C_8H_{12}O_2N_4S$: N, 24.54. Found: N, 24.46, 24.66.

This hydrazide is soluble in water (1 g. in 3 ml. hot and 10 ml. cold). Water is not recommended, however, as a solvent for purification as slight decomposition takes place in boiling solutions with evolution of ethyl mercaptan. Aqueous solutions of the hydrazide reduce Fehling's solution easily. The hydrazide is less soluble in absolute alcohol than in water (1 g. in 250 ml. hot and 450 ml. cold).

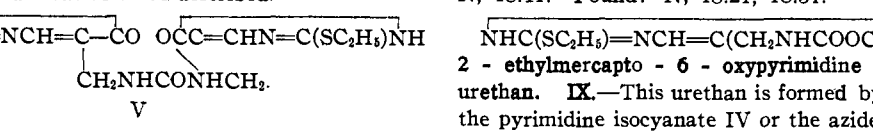
$\overline{NHC(SC_2H_5)=NCH=C(CH_2CON_3)CO}$. **2-Ethylmercapto-6-oxypyrimidine-5-acetylazide. III.**—The mercapto-pyrimidine hydrazide II reacts smoothly with nitrous acid to form this azide, III. Twenty grams of the purified hydrazide is dissolved in 200 ml. of normal hydrochloric acid. To this clear solution, cooled in an ice-bath, is then added slowly, while stirring, an aqueous solution containing the required amount of sodium or potassium nitrite. An immediate precipitate of a fluffy solid is obtained which, after washing with water and drying, weighed 12 g. At ordinary temperatures this azide is stable, but on heating to 75–80° it evolves nitrogen vigorously, and then melts with decomposition at 175–180°. The compound responded to the characteristic reactions of an azide, and underwent quantitative transformations giving the corresponding ethyl and benzyl urethans and also the pyrimidine isocyanate derivative when treated with the proper reagents or solvents.

$\overline{NHC(SC_2H_5)=NCH=C(CH_2NCO)CO}$. **2-Ethylmercapto-6-oxypyrimidine-6-methyl Isocyanate. IV.**—This interesting compound is easily prepared as follows: 2.4 g. of 2-ethylmercapto-6-oxypyrimidine-5-acetylazide is suspended in 20 ml. of dry toluene and the temperature of the heating bath slowly raised to about 80° when a vigorous evolution of nitrogen begins to take place. Too rapid heating leads to considerable decomposition and charring of the reaction product. When the violent evolution of nitrogen gas has ceased (twenty minutes) the toluene is then heated to its boiling point and the liquid finally refluxed for thirty minutes. At the end of this time, the toluene is cooled, and the insoluble isocyanate separated by filtration and washed with ether. The yield of crude material was 2.2 g. melting at 187–190° with decomposition. The isocyanate is purified by recrystallization from anhydrous dioxane, from which solvent it separates, on cooling, in the form of plates, which melt at 189–191° with decomposition. *Anal.* Calcd. for $C_8H_9O_2N_3S$: N, 19.90. Found: N, 19.74, 19.73.

This isocyanate is not appreciably soluble in the ordinary inert organic solvents and is unusually stable for an isocyanate compound. It underwent no detectable

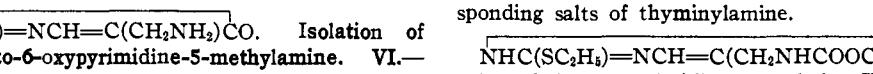
(7) Th. Curtius, *J. prakt. Chem.*, [2] **50**, 275 (1894); **58**, 190 (1898); **64**, 297, 401, 419 (1901); **91**, 1, 19 (1915); **94**, 85, 273 (1917); *Ber.*, **27**, 778 (1894).

change after preservation for five months in a tightly stoppered specimen tube. The compound responds to all the characteristic reactions of an isocyanate structure, and is a pyrimidine derivative which should prove very useful for future experimentation. It is the first mercapto-pyrimidine isocyanate derivative to be described.



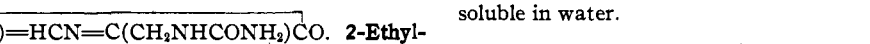
V

Behavior toward Water: Formation of *sym.*-Di-(ethylmercapto-6-oxypyrimidine-5-methyl)-urea. V.—The rate of decomposition of the above isocyanate IV in cold water is very slow. When, however, the compound is warmed with water there is a rapid evolution of carbon dioxide, and during the time of heating there is a brief period of almost complete solution followed immediately by the precipitation of the symmetrical disubstituted urea V. While this urea constitutes the main reaction product, small quantities of the normal amine VI are also obtained when the mother liquor is concentrated to a small volume. For example: 1 g. of the isocyanate is boiled with 40 ml. of water until the evolution of carbon dioxide ceases and the solution is then cooled. We obtained 0.63 g. of the above urea crystallizing in the form of prisms and melting at 270–272° with decomposition. The compound is practically insoluble in water, and all the common organic solvents. *Anal.* Calcd. for $C_{15}H_{20}O_3N_6S_2$: N, 21.20. Found: N, 21.21, 21.16.

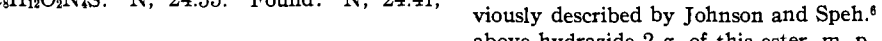


Isolation of 2-Ethylmercapto-6-oxypyrimidine-5-methylamine. VI.—The combined filtrates and washings from the preceding experiment were concentrated to a volume of 10 ml. and the solution cooled, when 0.07 g. of this amine separated. It melted at 220–222° with decomposition. This pyrimidine is easily purified by crystallization from boiling water, and separates, on cooling, in the form of colorless needles, melting at 221–222° with decomposition. Aqueous solutions of the amine are strongly basic to the mixed indicator (methyl red and methylene blue). *Anal.* Calcd. for $C_7H_{11}ON_3S$: N, 22.70. Found: N, 23.00, 23.10.

Hydrolysis of the above pyrimidine isocyanate VI by boiling with strong hydrochloric acid leads to the formation of the hydrochloride of thyminylamine with evolution of ethyl mercaptan and carbon dioxide.



2-Ethylmercapto-6-oxypyrimidine-5-methyl Urea. VII.—This is formed quantitatively by action of aqueous ammonia on the pyrimidine isocyanate IV. The pyrimidine is very soluble in cold water and alcohol. It was purified by dissolving in 95% alcohol and allowing the solution to evaporate in a vacuum desiccator. In this way the urea was obtained in the form of colorless plates melting at 190–192° with decomposition. A mixture of this urea with the original isocyanate melted at 175–176°. *Anal.* Calcd. for $C_8H_{12}O_2N_4S$: N, 24.55. Found: N, 24.41, 24.64.



2-Ethylmercapto-6-oxypyrimidine-5-methyl-phenylurea. VIII.—This is formed by the action of aniline on the pyrimidine isocyanate IV in hot dioxane solution. The urea is easily purified by crystallization from 95% alcohol and crystallizes in plates melting at 223–224° with decomposition. The urea can be crystallized from both dioxane and water. *Anal.* Calcd. for $C_{14}H_{16}O_2N_4S$: N, 18.41. Found: N, 18.21, 18.31.

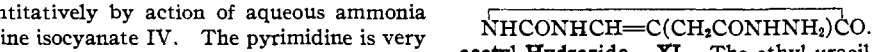
Ethyl-2-ethylmercapto-6-oxypyrimidine-5-methyl-urethan. IX.—This urethan is formed by interaction of the pyrimidine isocyanate IV or the azide III with ethyl alcohol. Ten grams of the pyrimidine azide (described above) is suspended in 50 ml. of absolute alcohol and the temperature of the alcohol gradually raised by heating on a water-bath. Nitrogen is evolved vigorously and after heating one hour the azide is completely decomposed and a clear solution is obtained. The alcohol solution is now concentrated to a volume in 10 ml. and cooled when the desired urethan will separate. The yield was about 9.0 g. and the compound melted at 145–148°, to a clear liquid. The pyrimidine is purified by crystallization from 95% alcohol and separates, on cooling, in the form of plates melting at 148.5–149.5° to a clear liquid. *Anal.* Calcd. for $C_{10}H_{15}O_3N_3S$: N, 16.34. Found: N, 16.37, 16.39.

When warmed in an alcohol solution of hydrochloric acid the corresponding 2-oxypyrimidine-urethan XV is formed with evolution of ethyl mercaptan. On heating with strong sulfuric or hydrochloric acid (100–110°) the urethan is decomposed with formation of the corresponding salts of thyminylamine.

Benzyl-2-ethyl-6-oxypyrimidine-5-methyl Urethan. X.—The pyrimidine-azide III is decomposed smoothly, when warmed in benzyl alcohol, with evolution of nitrogen and formation of the above urethan. After thirty minutes of heating in a hot water-bath the volume of the benzyl alcohol solution is reduced to about 10 ml. and then diluted with cold water. The urethan is precipitated as an oil which finally solidifies. The yield is excellent. By recrystallization from 95% alcohol the urethan is obtained in the form of needles melting at 159–160° to a clear oil. *Anal.* Calcd. for $C_{15}H_{17}O_3N_3S$: N, 13.17. Found: N, 13.33, 13.27.

This pyrimidine is very soluble in cold benzyl alcohol (1 g. in 4 ml.), moderately soluble in 95% alcohol and insoluble in water.

Part Two



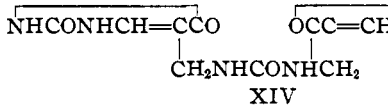
Uracil-5-acetyl Hydrazide. XI.—The ethyl uracil-5-acetate which was used for the synthesis of this hydrazide was prepared by dissolving the ethyl ester of 2-ethylmercapto-6-oxypyrimidine-5-acetic acid I in absolute alcohol, saturating with hydrogen chloride gas and then refluxing the solution for two hours. The ester separated, on cooling, and agreed in all its properties with the pyrimidine ester previously described by Johnson and Speh.[6] To prepare the above hydrazide 2 g. of this ester, m. p. 202–204°, is dissolved in 30 ml. of 95% alcohol, and to the hot solution 1.5 g. of hydrazine hydrate is added. After refluxing for one hour and cooling for twelve hours 1.8 g. of the hydra-

zide separated. It is easily purified by recrystallization from boiling water and crystallizes in the form of plates which decompose without melting at about 326°, turning brown at 285°. The compound is insoluble in alcohol and the common organic solvents. Aqueous solutions of the hydrazide reduce Fehling's solution immediately. *Anal.* Calcd. for $C_6H_8O_3N_4$: C, 39.13; H, 4.40. Found: C, 39.15, 39.25; H, 4.41, 4.32.

$\overline{\text{NHCONHCH=C(CH}_2\text{CON}_3)\text{CO}}$. **Uracil-5-acetyl-azide. XII.**—Four grams of the above hydrazide XI is dissolved in 100 ml. of *N* hydrochloric acid and 1.5 equivalents of sodium nitrite dissolved in the solution. There is an immediate reaction and the azide separates at once as a colorless powder. This is stable at room temperatures, but loses nitrogen when heated at 75–80° and then melts at 275–276° with decomposition. Although this pyrimidine was not analyzed, its structure was proved by its characteristic chemical behavior, yielding both urethan derivatives and the corresponding isocyanate, XIII.

$\overline{\text{NHCONHCH=C(CH}_2\text{NCO)CO}}$. **Uracil-5-methyl Isocyanate (Thyminyl Isocyanate). XIII.**—This isocyanate was prepared according to the same technique as was used for the preparation of 2-ethylmercapto-6-oxypyrimidine-5-methyl isocyanate IV: 1.8 g. of uracil-5-acetyl azide XII yielded, when heated in toluene, 1.4 g. of the isocyanate as a colorless powder which melts at 273–275° with decomposition. *Anal.* Calcd. for $C_6H_5O_3N_3$: N, 25.15. Found: N, 25.15, 24.90.

$\overline{\text{NHCONHCH=CCO}}$ $\overline{\text{OCC=CHNHCONH}}$. **Behavior toward Water: Formation of *sym.*-Di-thyminylurea. XIV.**—Boiling water immediately decomposes thyminyl isocyanate XIII with vigorous evolution of carbon dioxide; 0.3 g. of this pyrimidine of m. p. 273–275°, after boiling for twenty minutes in 20 ml. of water, yielded 0.25 g. of this urea derivative. This is very insoluble in water and decomposes without further purification at 315°. *Anal.* Calcd. for $C_{11}H_{12}O_5N_6$: N, 27.26. Found: N, 27.09, 27.14.



XIV

$\overline{\text{NHCONHCH=C(CH}_2\text{NHCOOC}_2\text{H}_5)\text{CO}}$. **Ethyl Thyminyl-urethan. XV.**—Five grams of ethyl 2-ethylmercapto-6-oxypyrimidine-5-methylurethan is dissolved in 50 ml. of 95% alcohol acidified with 5 ml. of concentrated hydrochloric acid. As soon as this solution is warmed, ethyl mercaptan is evolved, and within twenty-five minutes the urethan begins to crystallize from the hot solution, and the hydrolysis is practically complete. We obtained 3.4 g. of the above urethan melting at 254–258°. It is easily purified by crystallization from 95% alcohol and melts at 256–257° to a clear oil. The compound is more soluble in water than in alcohol. *Anal.* Calcd. for $C_8H_{11}O_4N_3$: N, 19.72. Found: N, 19.74.

This same urethan is also obtained in excellent yield by digesting uracil-5-acetylazide in absolute alcohol. When digested with either hydrochloric or sulfuric acid it is converted into the corresponding salts of thyminylamine.

$\overline{\text{NHCONHCH=C(CH}_2\text{NHCOOC}_7\text{H}_7)\text{CO}}$. **Benzyl Thyminyl-urethan. XVI.**—When 0.8 g. of benzyl 2-ethylmercapto-6-oxypyrimidine-5-methylurethan was digested in alcohol acidified with hydrochloric acid for two hours, 0.5 g. of this urethan was formed. This is less soluble in alcohol than the corresponding mercapto compound X, and separates from this solvent in the form of microscopic plates which melt at 261–263° with decomposition. *Anal.* Calcd. for $C_{13}H_{13}O_4N_3$: N, 15.27. Found: N, 15.35, 15.55.

Summary

1. Starting with the known pyrimidine, ethyl-2-ethylmercapto-6-oxypyrimidine-5-acetate, several new derivatives have been synthesized by application of the Curtius reaction for replacement of the carbethoxy group by an amino radical.

2. Important new aliphatic derivatives of uracil have been described which will find use in developing new synthetic processes of biochemical interest.

3. A practical method is revealed for preparing uracil-5-methyl isocyanate or thyminyl isocyanate, the first isocyanate derivative to be described in the pyrimidine series.

4. Further applications of the Curtius reaction in the pyrimidine series will be made, and further synthetic work of biological interest is now in progress in this Laboratory.

NEW HAVEN, CONNECTICUT RECEIVED JULY 25, 1936