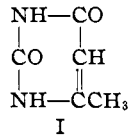
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, YALE UNIVERSITY]

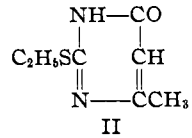
Interaction of Chloromethyl Ether with Pyrimidines.[1] I

BY MARGARET M. ENDICOTT[2] AND TREAT B. JOHNSON

In a previous paper from this Laboratory[3] attention was called to the significance of the skeleton structure of *thiamine*, and the relationship of this vitamin principle to the pyrimidine, *thymine*. Methods for converting uracil into side chain derivatives of thymine were studied and it was stated that the investigation of other methods for introducing methylene groupings into pyrimidines in position-5 would be continued. Previous investigations showing that certain pyrrole[4] pyrroporphyrins[5] and benzene[6] as well as other cyclic compounds[7] react with α-halogenated ethers, suggested that chloromethyl ether might react with the pyrimidine cycle. The present investigation was undertaken in the hope that it would be possible to obtain primary pyrimidine halides ($R{\cdot}CH_2Cl$) with substitution in the 5-position of the cycle by means of the interaction of chloromethyl ether with certain readily available pyrimidine constructions. Pyrimidine derivatives of this type are difficult to prepare and are of special interest at the present time because of their structural relationship to the pyrimidine (IV), employed in the practical synthesis of thiamine (vitamin B_1).[8] The pyrimidines studied were 4-methyluracil (I), 2-ethylmercapto-4-methyl-6-oxypyrimidine (II), and 2,6-dichloro-4-methylpyrimidine (III). Isomeric pyrimidine halides containing the halide grouping ($\cdot CH_2Cl$) in the 4-position of the pyrimidine ring have previously been synthesized in this Laboratory.[9]



I



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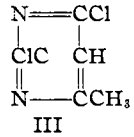
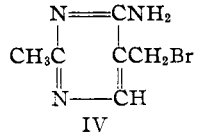


III



IV

All of the experiments reported in this paper to determine the behavior of chloromethyl ether toward pyrimidines I, II and III were conducted in glacial acetic acid solution as recommended by Vavon and Bolle.[7] In no case did the authors succeed in isolating a pyrimidine derivative containing the grouping ($\cdot CH_2Cl$); however, results of great interest were obtained.

Chloromethyl ether and all the halogenated pyrimidines incorporated in our research were decomposed with generation of hydrochloric acid when exposed to the action of glacial acetic acid.

Experimental Part

Action of Chloromethyl Ether on 2-Ethylmercapto-4-methyl-6-oxypyrimidine II in Cold Glacial Acetic Acid Solution.[10]—The addition of freshly distilled chloromethyl ether (5.3 g. or 1.1 mols) to a solution of 10 g. of this 2-mercaptopyrimidine in 40 ml. of cold glacial acetic acid caused an immediate precipitate of its hydrochloric acid salt. After allowing the reaction mixture to stand in a stoppered flask at room temperature for five hours, 12.22 g. had separated. This was increased to 12.99 g. by the addition of anhydrous ether to the mother liquor. In two subsequent experiments the reaction mixture was sealed in an ampule and then allowed to stand at room temperature for thirty-seven and fifty days, respectively. During these periods the precipitate of the pyrimidine hydrochloride gradually changed from plate-like crystals to large transparent prisms. This represented, however, only a physical change in the crystalline habit of the salt. This same salt is also formed by dissolving the 2-ethylmercapto-4-methyl-6-oxypyrimidine in concentrated hydrochloric acid by gentle warming. The salt crystallizes in large transparent prisms which melt with evolution of gas to a clear liquid at 170.5–172°. The salt dissolved in cold absolute ethanol and is difficultly soluble in cold glacial acetic acid and cold water. It is purified by crystallization from concentrated hydrochloric acid or by dissolving in cold absolute ethanol and precipitating with absolute ether. In both cases the salt crystallizes with one mole of water of crystallization which it loses when heated in a vacuum at 100°.

(1) Researches on Pyrimidines, CLXX. This paper was constructed from a dissertation presented by Miss Margaret M. Endicott in June, 1939, to the Graduate Faculty of Yale University in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(2) Yale University Fellow in Chemistry, 1938–1939.

(3) Researches on Pyrimidines. CLXIV, Riehl and Johnson, *Rec. trav. chim.*, **59**, 87 (1940).

(4) W. Kuster, *Z. physiol. Chem.*, **121**, 146 (1922); H. Fischer and E. Adler, *ibid.*, **197**, 252, 276 (1931).

(5) H. Fischer and H. Riedl, *Ann.*, **486**, 178 (1931).

(6) M. Sommelet, *Compt. rend.*, **157**, 1443 (1913).

(7) G. Vavon and J. Bolle, *ibid.*, **204**, 1826 (1937).

(8) R. R. Williams and J. K. Cline, THIS JOURNAL, **58**, 1504 (1936); J. K. Cline, R. R. Williams and J. Finkelstein, *ibid.*, **59**, 1052 (1937).

(9) T. B. Johnson and L. Chernoff, *ibid.*, **36**, 1742 (1914); **35**, 585 (1913); *J. Biol. Chem.*, **14**, 307 (1913).

(10) (a) The authors did not investigate the action of chloromethyl ether on this mercaptopyrimidine in boiling acetic acid, since results obtained in a preliminary experiment indicated that such experimental conditions favored the formation of a mixture of reaction products presenting unexpected difficulties in purification. (b) C. Johns, *Am. Chem. J.*, **40**, 350 (1908).

Anal. (a) Calcd. for $C_7H_{10}ON_2S \cdot HCl \cdot H_2O$: N, 12.43; Cl, 15.78. Found: N, 12.27, 12.29, 12.32. Cl, 15.78, 15.61. (b) Calcd. for $C_7H_{10}ON_2S \cdot HCl$: N, 13.51. Found: N, 13.61, 13.67.

When a cold aqueous suspension of the hydrochloride was treated with dilute ammonium hydroxide, it was converted to the free base, since the product, when mixed with a pure sample of 2-ethylmercapto-4-methyl-6-oxypyrimidine, caused no depression in the melting point of this substance. Two grams of the above hydrochloride was heated in an oil-bath at 190–195° until the evolution of gaseous products ceased. Both ethyl mercaptan and hydrochloric acid were generated copiously. On cooling, a hard, yellow cake remained which proved to be a mixture of **2-thio-4-methyl-6-oxypyrimidine**[11] and **4-methyluracil** I (m. p. 314–316°). The great difference in the solubility of these two compounds in boiling water made it possible to separate them by fractional crystallization from that solvent. The 2-thiopyrimidine decomposed above 285°.

Anal. Calcd. for $C_5H_6ON_2S$: N, 19.72. Found: N, 19.66, 19.62.

It is interesting to note here that the tendency of 2-mercapto-6-oxypyrimidines to form hydrochlorides has not been investigated. Only one compound of this type has been described. This was formed by passing chlorine gas into an acetic acid solution of 2-ethylmercapto-6-oxypyrimidine and was obtained instead of the expected 2-methylmercapto-5-chloro-6-oxypyrimidine.[12]

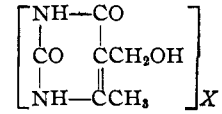
Action of Chloromethyl Ether on 2,6-Dichloro-4-methylpyrimidine,[13] III. A. In Cold Glacial Acetic Acid Solution.—Five grams of 2,6-dichloro-4-methylpyrimidine and 2.7 g. (1.1 mols) of chloromethyl ether were dissolved in 20 ml. of glacial acetic acid solution and the solution allowed to stand in a sealed ampule at room temperature. At the end of twenty-four hours a crystalline substance began to form and this increased slowly on standing. At the end of twenty-five days the ampule was opened and the pressure of hydrochloric gas released. The crystalline deposit was then removed by filtration and treated as follows.

Repeated washing of this product with ether removed 0.68 g. of colorless crystals which melted at 45–47° and was identified as unaltered 2,6-dichloro-4-methylpyrimidine. The residue, insoluble in ether (0.72 g.) was purified by recrystallization from boiling, alcohol-free dioxane from which it separated on cooling in fine feathery crystals which decomposed above 275°. This was identified as the hydrochloride of **2-chloro-4-methyl-6-oxypyrimidine.**[14]

Anal. Calcd. for $C_5H_5ON_2Cl \cdot HCl$: N, 15.48. Found: N, 15.60, 15.65.

This hydrochloride, which is difficult to handle because of its instability, dissolves in hot ethanol with decomposition forming **2-ethoxy-4-methyl-6-oxypyrimidine** hydrochloride (see below). It is insoluble in ether and glacial acetic acid.

The acetic acid filtrate (above) was concentrated "*in vacuo*" over soda-lime. There was finally obtained after four to five days a dry cake weighing 3.64 g. which did not melt or decompose below 340°. It was free from unreacted 2,6-dichloro-4-methylpyrimidine and was purified by crystallization from boiling water, in which it was difficultly soluble and finally dried for analysis in a vacuum desiccator. A more convenient method of purification consisted in dissolving the pyrimidine in cold dilute alkali and precipitating it in the form of a powder by addition of the required amount of 6 *N* hydrochloric acid. Because of its extreme insolubility in all solvents it was not possible to determine its molecular weight. Analytical determinations agreed with the calculated value for a "polymer" of 5-oxymethyl-4-methyluracil, represented by formula VI.



VI

Anal. Calcd. for $(C_6H_8O_3N_2)_x$: N, 17.96. Found: N, 17.83, 18.01, 17.89, 17.85.

$\overline{NH—C(OC_2H_5)=N—C(CH_3)=CH—CO}$, **2-Ethoxy-4-methyl-6-oxypyrimidine.**—This pyrimidine was obtained in the form of its hydrochloride by dissolving the hydrochloride of 2-chloro-4-methyl-6-oxypyrimidine in boiling absolute ethanol. The salt was precipitated from the alcohol solution by dilution with ether. After recrystallization from a mixture of ether and absolute ethanol it decomposed at 312–314°.

Anal. Calcd. for $C_7H_{10}O_2N_2 \cdot HCl$: N, 14.70. Found: N, 14.62, 14.60.

Treatment of this hydrochloride with an equivalent amount of sodium carbonate solution gave a quantitative yield of the free pyrimidine base. This was purified by crystallization from hot water and separated in the form of glistening prisms melting at 206–207°. When mixed with a sample of 2-ethoxy-4-methyl-6-oxypyrimidine prepared by condensing ethylpseudourea with ethyl acetoacetate[15] no depression of the melting point was observed.

B. In Hot Glacial Acetic Acid Solution.—The pyrimidine "polymer" VI was formed by refluxing a solution of 5 g. of 2,6-dichloro-4-methylpyrimidine and 3 g. (1.2 mols) of chlormethyl ether in 20 ml. of glacial acetic acid for seven hours. The total yield was 4.67 g. or 98%. The "polymer" did not melt below 340° and was purified in the manner already described.

Anal. Calcd. for $(C_6H_8O_3N_2)_x$: N, 17.96. Found: N, 17.90, 18.10, 17.98, 18.11.

Reduction of the "Polymer" or 5-Oxymethyl-4-methyluracil VI.—Two grams of the "polymer" VI, 0.5 g. of red phosphorus, 15 ml. of hydriodic acid (sp. gr. 1.7) and 15 ml. of glacial acetic acid were refluxed together for two hours. After evaporating the reaction mixture to dryness, the

(11) R. List, *Ann.*, **236**, 14 (1886).

(12) H. L. Wheeler and H. B. Bristol, *Am. Chem. J.*, **33**, 447 (1905).

(13) S. Gabriel and J. Colman, *Ber.*, **32**, 1533 (1899).

(14) It has not been possible to explain satisfactorily the mechanism for the formation of this hydrochloride from 2,6-dichloro-4-methylpyrimidine. When the latter was allowed to stand for several days in a sealed ampule dissolved in either glacial acetic acid or in glacial acetic acid into which dry hydrogen chloride gas had been bubbled, a mixture of 4-methyluracil and unchanged 2,6-dichloro-4-methylpyridine was obtained. Therefore, neither the acetic acid nor the hydrogen chloride formed by the interaction of the chloromethyl ether and acetic acid was responsible for the formation of the 2-chloro-4-methyl-6-oxypyrimidine hydrochloride.

(15) W. I. Bruce, THIS JOURNAL, **26**, 455 (1904).

residue was treated with 15 ml. of cold water and again evaporated to dryness to remove the excess of hydriodic acid present. The residue then consisted of a mixture of 4,5-dimethyluracil, bis-(4-methyl-2,6-dioxypyrimidyl-5)-methane and red phosphorus. The 4,5-dimethyluracil (1.13 g.) was separated by aqueous extraction and purified by crystallization from hot water. It melted at 295–7° and when mixed with the synthetic product[16] caused no depression in the melting point.

Bis-(4-methyl-2,6-dioxypyrimidyl-5)-methane (0.52 g.) was separated from the red phosphorus by treating the residue (above) with dilute alkali, filtering and precipitating the bis-compound with acetic acid. This pyrimidine is insoluble in all solvents and was purified for analysis by dissolving it in dilute alkali and reprecipitating it with acetic acid. It did not show any change when heated at 340°.

Anal. Calcd. for $C_{11}H_{12}O_4N_4$: N, 21.20. Found: N, 20.95, 20.98.

This same bis-compound was also obtained in good yield by digestion of the "polymer" VI with concentrated hydrochloric acid for four hours. When thoroughly dried it tends to be strongly pyroelectric. This pyrimidine is not reduced by prolonged digestion with hydriodic acid and red phosphorus and also is not changed by treatment with fuming nitric acid (sp. gr. 1.51).

Action of Chloromethyl Ether on 4-Methyluracil I in Hot Glacial Acetic Acid.[17]—Two grams of 4-methyluracil and 2 g. (1.7 mols) of chloromethyl ether were dissolved in 30 ml. of boiling glacial acetic acid to give a clear solution. This was refluxed for two and one-half hours during which the formation of a white solid gradually took place and hydrogen chloride gas was evolved constantly from the reaction mixture. The weight of the insoluble material, filtered off after cooling, was 0.74 g. It did not melt below 340° and was identified as bis-(4-methyl-2,6-dioxypyrimidyl-5)-methane.

Anal. Calcd. for $C_{11}H_{12}O_4N_4$: N, 21.20. Found: N, 21.22, 21.10.

The acetic acid filtrate (above) was evaporated to about one-third of its original volume and then diluted with ether, when 2.0 g. of a crystalline product was obtained. This was easily purified by recrystallization from boiling acetic acid from which it separated in the form of prisms. This material shriveled at 233° and decomposed with effervescence at 320°. The compound is moderately soluble in boiling water, but it decomposes if its aqueous solution is heated for any length of time. It is slightly soluble in boiling absolute ethanol and insoluble in ether. A nitrogen determination agreed with the calculated value for 5-acetoxymethyl-4-methyluracil which was proved to be the correct structure for this compound since it was readily reduced to 4,5-dimethyluracil (below).

Anal. Calcd. for $C_8H_{10}O_4N_2$: N, 14.14. Found: N, 13.92, 13.95.

The investigation of the action of methoxymethyl acetate on 4-methyluracil, and the condensation of 5-acetoxymethyl-4-methyluracil with 4-methyluracil showed that the above reaction could be interpreted in the following way: (1) the formation of 5-acetoxymethyl-4-methyluracil by the condensation of 4-methyluracil with methoxymethyl acetate, formed by the interaction of chloromethyl ether and acetic acid, (2) the reaction of this initial product with some unchanged 4-methyluracil to give bis-(4-methyl-2,6-dioxypyrimidyl-5)-methane.

Action of Methoxymethyl Acetate on 4-Methyluracil in Hot Glacial Acetic Acid.—A solution of 2 g. of 4-methyluracil and 2.8 g. (1.7 mols) of methoxymethyl acetate[18] in 30 ml. of boiling glacial acetic acid, into which dry hydrogen chloride gas had been bubbled for a few minutes,[19] was refluxed for two and one-half hours. The products of the reaction of 1.14 g. of bis-(4-methyl-2,6-dioxypyrimidyl-5)-methane (a) and 1.25 g. of 5-acetoxymethyl-4-methyluracil (b) were separated in the manner described in the preceding experiment.

Anal. (a) Calcd. for $C_{11}H_{12}O_4N_4$: N, 21.20. Found: N, 21.20, 20.98. (b) Calcd. for $C_8H_{10}O_4N_2$: N, 14.14. Found: N, 14.22, 14.30.

Condensation of 4-Methyluracil with 5-Acetoxymethyl-4-methyluracil.—Equivalent quantities of 4-methyluracil (2 g.) and 5-acetoxymethyl-4-methyluracil (3.14 g.) were dissolved in 50 ml. of boiling glacial acetic acid, partially saturated with dry hydrogen chloride gas. This was refluxed for 7.5 hours when 3.72 g. of bis-(4-methyl-2,6-dioxypyrimidyl-5)-methane was separated from the acetic acid solution by filtration. The mother liquor was then partially saturated again with dry hydrogen chloride and the digestion continued for four hours. This increased the total yield of the bis-pyrimidine to 4.09 g. or 98% of the theoretical yield. The pyrimidine was purified as described above.

Anal. (a) Calcd. for $C_{11}H_{12}O_4N_4$: N, 21.20. Found: N, 21.14, 21.11.

Reduction of 5-Acetoxymethyl-4-methyluracil with Hydriodic Acid.—Two grams of 5-acetoxymethyl-4-methyluracil, 0.5 g. of red phosphorus, 10 ml. of hydriodic acid (sp. gr. 1.7) and 15 ml. of glacial acetic acid were refluxed together for one hour and the reaction mixture was then evaporated to dryness. The residue was treated in the manner already described for the separation of a similar mixture obtained in the reduction of the "insoluble polymer" VI. This resulted in the separation of 0.21 g. of bis-(4-methyl-2,6-dioxypyrimidyl-5)-methane (a) and 1.29 g. of 4,5-dimethyluracil (b). The latter, after recrystallization from boiling water, melted at 296–298° and, when mixed with a pure specimen of 4,5-dimethyluracil, caused no depression in the melting point.

Anal. (a) Calcd. for $C_{11}H_{12}O_4N_4$: N, 21.20. Found: N, 21.18, 21.07.

Summary

1. The action of chloromethyl ether on 4-methyluracil, 2-ethylmercapto-4-methyl-6-oxypyrimidine and 2,6-dichloro-4-methylpyrimidine in glacial acetic acid solution has been investigated.

(16) H. Wheeler and H. Merriam, *Am. Chem. J.*, **29**, 489 (1903).

(17) Since 4-methyluracil is only slightly soluble in cold glacial acetic acid, its behavior toward chloromethyl ether under these conditions has not been investigated.

(18) F. Clark, S. Cox and E. Mack, THIS JOURNAL, **39**, 714 (1917).

(19) When this experiment was carried out in the absence of hydrogen chloride, no reaction took place.

2. The 2-ethylmercapto-4-methyl-6-oxypyrimidine is converted quantitatively into its characteristic hydrochloride without any evidence of the introduction of the grouping ($\cdot CH_2Cl$) into the pyrimidine ring.

3. 2,6-Dichloro-4-methylpyrimidine interacts with the chloromethyl ether to form 2-chloro-4-methyl-6-oxypyrimidine and a polymeric modification of 5-oxymethyl-4-methyluracil. Reduction of this "polymer" with hydriodic acid leads to the formation of (a) 4,5-dimethyluracil and (b) bis-(4-methyl-2,6-dioxypyrimidyl-5)-methane.

4. 4-Methyluracil and the chloromethyl ether interact to form bis-(4-methyl-2,6-dioxypyrimidyl-5)-methane and 5-acetoxymethyl-4-methyluracil.

5. Vavon and Bolle[7] have interpreted the interaction of chloromethyl ether with aromatic hydrocarbons in acetic acid solution as a simple double decomposition with elimination of methanol and substitution of the grouping ($\cdot CH_2Cl$). The evidence produced in the authors experimentation indicates that the active reagent under these conditions is $CH_3COOCH_2OCH_3$ rather than CH_3OCH_2Cl, and that the mechanism of reaction in these changes is more complex than Vavon and Bolle postulated.

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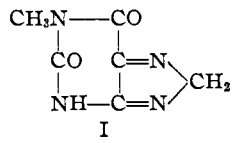
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, YALE UNIVERSITY]

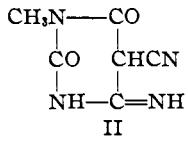
Researches on Pyrimidines. Derivatives of Pyrimidine-5-carboxylic Acid[1,2]

BY JOSEPH C. AMBELANG[3] AND TREAT B. JOHNSON

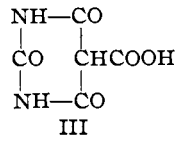
Following the failure of the authors[4] to synthesize a compound resembling in structure that proposed for *toxoflavine*[5] (I) the possibility of the isomeric structure (II) was next considered. The latter compound may be regarded as a methylated imidonitrile of 2,4,6-triketo-hexahydropyrimidine-5-carboxylic acid (III).



I

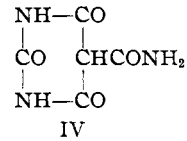


II

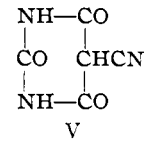


III

Although this acid (III) appears not to be recorded in the literature, its acid amide (IV) was prepared by Baeyer[6] in 1865; later by two other workers[7] and was named *malobiursäure* because it was formed by heating barbituric acid with fused urea.

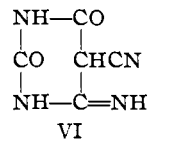


IV

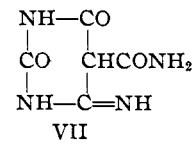


V

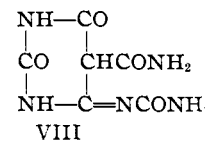
Since the 5-cyanobarbituric acids are unknown, the authors sought to prepare a member of this series to find out whether its reactions resembled the unusual behavior of *toxoflavine*.[5] The synthesis of 5-cyanobarbituric acid (V) and its 4-imido derivative (VI) was attempted according to the usual technique namely, by condensation of urea or thiourea with esters of cyanomalonic acid and dicyanoacetic acid, respectively.



VI



VII



VIII

No product suggestive of a barbiturate was isolated. When thiourea was heated with methyl dicyanoacetate in the presence of sodium ethylate there was formed a very small quantity of an unidentified product, acidic in nature, containing sulfur and nitrogen, but much too low a percentage of the latter element to be the expected pyrimidine.

The failure of these esters to condense under the experimental conditions employed for the preparation of barbiturates is not inconsistent

(1) The support of the Rockefeller Foundation of New York in this work is gratefully acknowledged by the authors.

(2) Presented in part before the Organic Division of the American Chemical Society at Cincinnati, Ohio, April 10, 1940.

(3) Sterling Professorship of Chemistry Research Assistant, 1939–40. Present address, D'Youville College, Buffalo, New York.

(4) Johnson and Ambelang, THIS JOURNAL, **61**, 2483 (1939).

(5) van Veen and Baars, *Proc. Koninkl. Akad. Wetenschappen*, **40**, 498 (1937).

(6) Baeyer, *Ann.*, **135**, 312 (1865).

(7) Nencki, *Ber.*, **5**, 888 (1872); Curtius, *ibid.*, **56**, 1579 (1923).